EFFICACY OF PREMIXED VERSUS SEQUENTIAL ADMINISTRATION OF CLONIDINE AS AN ADJUVANT TO HYPERBARIC BUPIVACAINE INTRATHECALLY IN CAESAREAN SECTION

Dissertation submitted to

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In partial fulfillment for the award of the degree of

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IN

ANAESTHESIOLOGY

BRANCH X

DEPARTMENT OF ANAESTHESIOLOGY

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CERTIFICATE

This is to certify that the dissertation entitled, **"EFFICACY OF PREMIXED VERSUS SEQUENTIAL ADMINISTRATION OF CLONIDINE AS AN ADJUVANT TO HYPERBARIC BUPIVACAINE INTRATHECALY IN CAESAREAN SECTION"**, submitted by **Dr.S.THANGADURAI** in partial fulfilment for the award of the degree of **Doctor of Medicine in Anaesthesiology** by the Tamilnadu Dr.M.G.R. Medical University, Chennai is a bonafide record of the work done by him in the Department of Anaesthesiology, Government Thanjavur medical College, during the academic year 2012-2015.

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I, **DR.S.THANGADURAI**, solemnly declare that the dissertation titled **"EFFICACY OF PREMIXED VERSUS SEQUENTIAL ADMINISTRATION OF CLONIDINE AS AN ADJUVANT TO HYPERBARIC BUPIVACAINE INTRATHECALY IN CAESAREAN SECTION",** is a bonafide work done by me at Thanjavur Medical College Hospital, Thanjavur, during 2012-2015.

The dissertation is submitted to **"The Tamilnadu Dr. M.G.R. Medical University, Chennai",** Tamilnadu as a partial fulfillment for the requirement of **M.D** Degree examinations – Branch -X (Anaesthesiology) to be held in April 2015.

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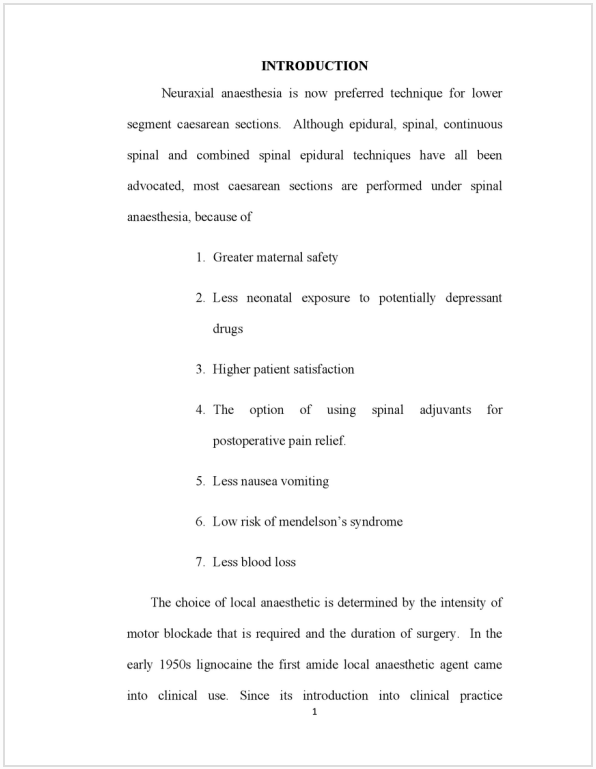

INTRODUCTION

Neuraxial anaesthesia is now preferred technique for lower segment caesarean sections. Although epidural, spinal, continuous spinal and combined spinal epidural techniques have all been advocated, most caesarean sections are performed under spinal anaesthesia, because of

1. Greater maternal safety
2. Less neonatal exposure to potentially depressant drugs
3. Higher patient satisfaction
4. The option of using spinal adjuvants for postoperative pain relief.
5. Less nausea vomiting
6. Low risk of mendelson's syndrome
7. Less blood loss

The choice of local anaesthetic is determined by the intensity of motor blockade that is required and the duration of surgery. In the early 1950s lignocaine the first amide local anaesthetic agent came into clinical use. Since its introduction into clinical practice

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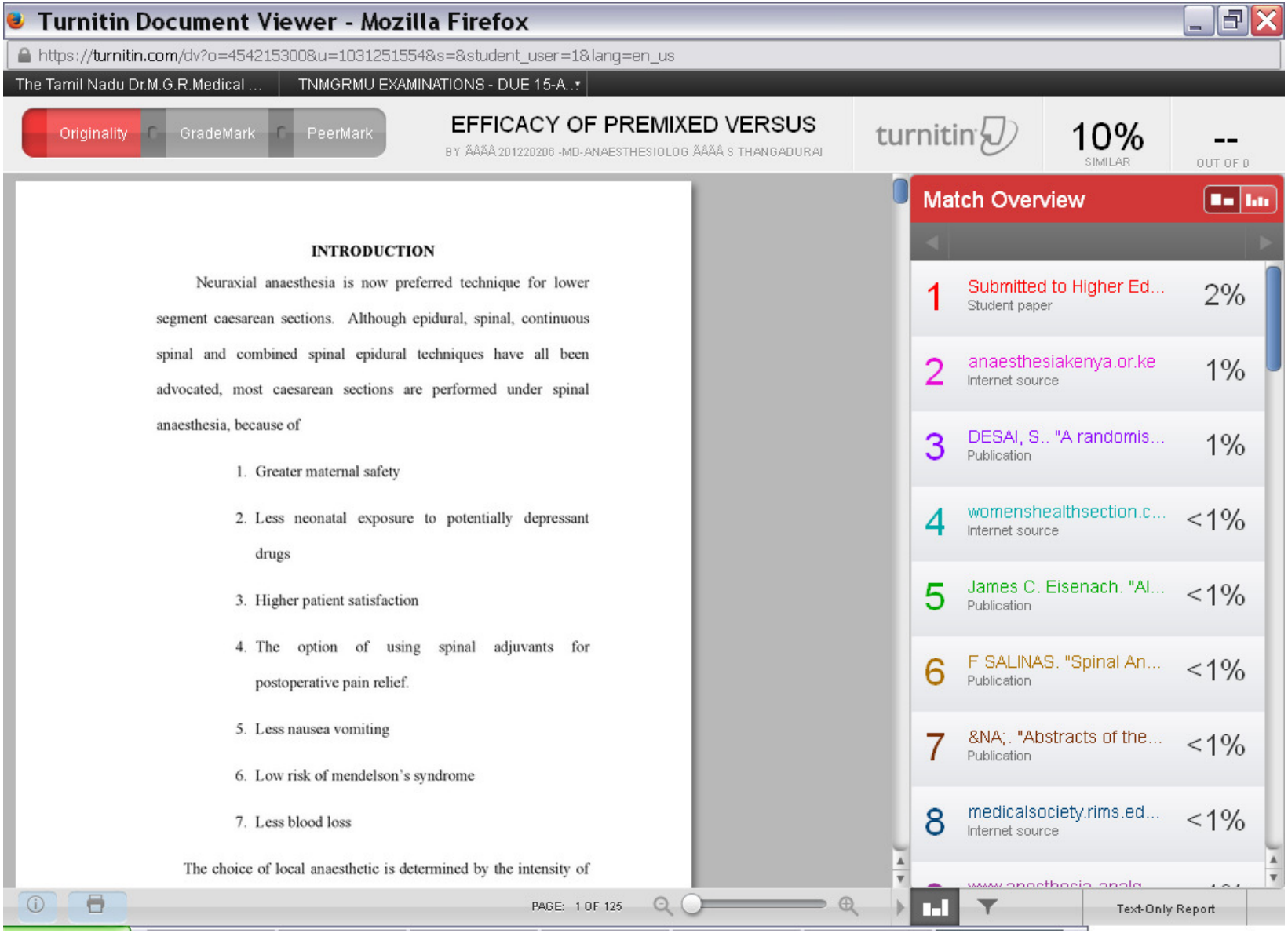
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CONTENTS

S.NO	TITLE	PAGE NO
1	INTRODUCTION	1
2	AIM OF THE STUDY	5
3	ANATOMY OF SPINAL CORD	6
4	PHYSIOLOGY OF SPINAL BLOCKADE	19
5	PHARMACOLOGY OF CLONIDINE	33
6	PHARMACOLOGY OF BUPIVACAINE	44
7	REVIEW OF LITRATURE	54
8	MATERIALS AND METHODS	69
9	STATISTICAL TOOLS	77
10	OBSERVATION AND RESULTS	78
11	DISCUSSION	102
12	SUMMARY	109
13	CONCLUSION	111
14	BIBLIOGRAPHY	
15	PROFORMA	
16	MASTER CHART	

ABSTRACT

Background and Aims: Mixing adjuvants with hyperbaric bupivacaine in a single syringe before injecting the drugs intrathecally is an age old practice. In doing so, the density of the hyperbaric solution and also of the adjuvant drugs may be altered, thus affecting the spread of drugs. Administering local anaesthetic and the adjuvants separately may minimise the effect of the changes in densities. We aimed to compare block characteristics, intraoperative haemodynamics and post-operative pain relief in parturients undergoing caesarean section (CS) after administering hyperbaric bupivacaine and clonidine intrathecally as a mixture and sequentially.

Methods: In this single-blind prospective randomised controlled study at a tertiary care centre from 2012 to 2015, 60 full-term parturients scheduled for elective caesarean sections were divided into two groups on the basis of technique of intrathecal drug administration. Group M received mixture of clonidine (75 mcg) and hyperbaric bupivacaine 0.5% (10 mg) intrathecally, whereas Group B received clonidine (75 mcg) followed by hyperbaric bupivacaine 0.5% (10 mg) through separate syringes. Observational descriptive statistics, independent t test were used as applicable.

Results: Duration of analgesia was significantly longer in Group B (432.60 ± 64.65 min) in which the drug was given sequentially than in Group M (322 ± 23.24 min). Furthermore, the time to achieve highest sensory block and complete motor block was significantly less in Group B without any major hemodynamic instability and neonatal outcome. **Conclusions:** When clonidine and hyperbaric bupivacaine were administered in a sequential manner, block characteristics improved significantly compared to the administration of the mixture of the two drugs.

Key words: Adjuvants, caesarean section, clonidine, hyperbaric bupivacaine, spinal anaesthesia

INTRODUCTION

Neuraxial anaesthesia is now preferred technique for lower segment caesarean sections. Although epidural, spinal, continuous spinal and combined spinal epidural techniques have all been advocated, most caesarean sections are performed under spinal anaesthesia, because of

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The choice of local anaesthetic is determined by the intensity of motor blockade that is required and the duration of surgery. In the early 1950s lignocaine the first amide local anaesthetic agent came into clinical use. Since its introduction into clinical practice

lignocaine was extensively used for spinal anaesthesia, but now its use has been drastically reduced due to concerns regarding transient neurological symptoms. This prompted search for an alternative bupivacaine which is the first long acting amide local anaesthetic agent. This is the most commonly used long acting amide till now.

Even when a long acting local anaesthetic like bupivacaine is used, the duration of spinal anaesthesia is limited and higher doses of analgesics are required in the post-operative period. Therefore achieving a spinal anaesthesia that provides longer duration of postoperative analgesia is an attractive goal. Thus addition of adjuvants with hyperbaric bupivacaine has come in to clinical practice. The adjuvants gained widespread popularity as they reduce the amount of local anaesthetics and thus the incidence of side effects.

Opioids such as morphine, fentanyl, sufentanyl have been administered intrathecally as adjuvants to prolong and potentiate post-operative analgesia. They are associated with many side effects like nausea, vomiting, pruritis, urinary retention and late unpredictable respiratory depression.

Clonidine a selective partial agonist for alpha -2 adrenergic receptor is an attractive alternative to commonly used opioids and is known to increase both sensory and motor block of local anaesthetics.

Several studies have shown that clonidine also has antihyperalgesic effect and thus reduces postoperative analgesic requirement. Many factors contribute to the spread and action of local anaesthetic solution in vivo. These includes

1. pH and baricity of the local anaesthetic solution
2. Temperature of the local anaesthetic solution
3. Patient position during and after spinal injection
4. Volume of the drug injected
5. Height of the patient

Commonly adjuvants are mixed with local anaesthetics in the single syringe before injecting intrathecally because of its ease of administration. Mixing of these drugs changes the density of both drugs, thus affecting their spread in the cerebrospinal fluid (CSF). Density is known to influence the spread of local anaesthetics but the effect of adjuvant solution density on its movement in the CSF has not been studied extensively.

Therefore we hypothesized that if we administer local anaesthetics and adjutants separately, it may minimize the effect of the changes in the densities and also their actions.

Therefore we designed the study to compare the efficacy of sequential versus premixed administration of clonidine with hyperbaric bupivacaine for caesarean sections in terms of block charecteristics, intra operative hemodynamics and post-operative pain relief.

AIM OF THE STUDY

To compare the efficacy of intrathecal administration of hyperbaric bupivacaine and clonidine as a mixture and sequentially in lowersegment caesarean section in terms of

1. **Block characteristics**
2. **Intraoperative haemodynamics**
3. **Postoperative pain relief**

ANATOMY

The vertebral canal[2]

The spine consists of 33 vertebrae (7 cervical, 12 thoracic, 5 lumbar, 5 fused sacral, and 4 fused coccygeal), with the exception of C1, the cervical, thoracic, and lumbar vertebrae consist of a body anteriorly, two pedicles that project posteriorly from the body, and two laminae that connect the pedicles.

These structures form the vertebral canal, which contains the spinal cord, spinal nerves, and epidural space. The laminae give rise to the transverse processes that project laterally and the spinous process that project posteriorly.

The pedicles contain a superior and inferior vertebral notch through which the spinal nerves exit the vertebral canal. The superior and inferior articular processes arise at the junction of the lamina and pedicles and form joints with the adjoining vertebrae.

The first cervical vertebra (“atlas”) differs from this typical structure in that it does not have a body or a spinous process.

The spine of C7 is the first prominent spinous process encountered while running the hand down the back of the neck. The spine of T1 is the most prominent spinous process and immediately follows C7. The 12th thoracic vertebra can be identified by palpating the 12th rib and tracing it back to its attachment to T12. A line drawn between the iliac crests crosses the body of L5 or the L4-5 inter space.

The spinal cord gives rise to 31 pairs of spinal nerves, each composed of an anterior motor root and a posterior sensory root. The nerve roots are in turn composed of multiple rootlets. The portion of the spinal cord that gives rise to all of the rootlets of a single spinal nerve is called a cord segment.

The skin area innervated by a given spinal nerve and its corresponding cord segment is called a dermatome.

Because the spinal cord usually ends between L1 and L2, the thoracic, lumbar, and sacral nerve roots run increasingly longer distances in the subarachnoid space to get from their spinal cord segment of origin to the intervertebral foramen through which they exit. Those nerves that extend beyond the end of the spinal cord to their exit site are collectively known as the cauda equina.

Ligaments of vertebral column[3]

1)Supraspinous ligament

It is a strong, thick, fibrous band, connecting the apices of the spines from the seventh cervical vertebra to the sacrum. At the lumbar region it is thick and broad. In the cervical region it blends with neck ligaments.

2)Interspinous ligament

The interspinous ligament is a thin fibrous structure, connecting adjacent spines. The fibres are almost membranous and extend from the apex and upper surface of a lower spine towards the root and inferior surface of the next higher vertebra. These longitudinal fibres meet the supraspinous ligament posteriorly and tends to blend with the ligamentum flavum in front.

3)Ligamentum flavum

This consists of yellow elastic tissue. They extend between lamina from the anterior inferior surface of the upper lamina downwards to the anterior superior surface of the lower lamina. The

ligament thickness, distance to dura, and skin to dura distance vary with the area of vertebral canal.

Characteristics of ligamentum flavum at different vertebral level, site

Thickness of ligament (mm)

Cervical 1.5-3.0

Thoracic 3.0-5.0

Lumbar 5.0-6.0

Caudal 2.0-6.0

4)Posterior longitudinal ligament:

It extends along the posterior surfaces of vertebral bodies from which it is separated by the basivertebral veins

5)Anterior longitudinal ligament:

It runs along the anterior surface of vertebral bodies from C2 to sacrum.

Anatomy of the spinal cord[3]

At birth, the tip of the spinal cord lies at the level of the lower border of L3 and the dural sac at the third sacral vertebrae. After birth, the lengthening and growth of the cord, as well as the

meninges, continue to lag behind the growth of the bony vertebral column. At one year of age, the conus medullaris reaches the lower border of the second lumbar vertebra and the dural sac ends at the second sacral vertebra. This differential growth rate results in the development of the epidural space and the caudal canal.

Between 12-16 years of age, the adult relations are attained, and the spinal cord is located at the lower border of the 1st lumbar vertebrae. This placement is seen in 50% of patient and in about 40% it is located opposite the body of second lumbar vertebrae.

The average length of the spinal cord in males is about 45 cms, and in females it is about 42 centimetres. The average weight is approximately 30 grams.

Meningeal coverings of the spinal cord[1,3]

Surrounding the spinal cord in the bony vertebral column are three membranes (from within to the periphery): the pia mater, arachnoid mater and dura mater.

Dura mater

This layer is the direct extension of the cranial dura mater and extends as spinal dura mater from the foramen magnum to S2, where the filum terminale blends with the periosteum on the coccyx.

Arachnoid mater

This is the middle of the three coverings of the brain and spinal cord. It is a delicate non-vascular membrane closely attached to the dura and ends at the lower border of S2.

Pia mater

This is a delicate, highly vascular membrane, closely investing the spinal cord and brain. Denticulate ligaments are the folds of pia mater that extends laterally along the lines of attachments of the anterior and posterior roots. They act as struts to hold the spinal cord suspended within the subdural space.

Dural spaces[1]

In the subarachnoid space are the CSF, spinal nerves and blood vessels that supply the spinal cord and the lateral extensions of the pia mater and the dentate ligaments, which supply lateral support from the spinal cord to the dura mater.

Although the spinal cord ends at the lower border of L1 in adults, the subarachnoid space continues to S2. There is a potential space between the dura mater and the arachnoid, the subdural space, which contains only small amounts of serous fluid allowing the dura and arachnoid to move over each other.

Surrounding the dura mater is the spinal epidural space extends from the foramen magnum to the sacral hiatus. The epidural space is bounded anteriorly by the posterior longitudinal ligaments, laterally by the pedicles and the intervertebral foramina, and posteriorly by the ligamentum flavum.

Contents of the epidural space include the nerve roots that traverse it from foramina to peripheral locations, as well as fat, areolar tissue, lymphatics, and blood vessels which include the well-organized Batson venous plexus.

Circulation of the Spinal Cord[3]

Arterial supply to the Spinal Cord

The principal arterial supply to the spinal cord is derived from one anterior and two pairs of posterior spinal arteries that descend from the level of the foramen magnum.

The anterior spinal artery is formed at the foramen magnum by a branch from the terminal portion of each vertebral artery. This is a large artery and lies in the midline on the anterior median fissure. It descends the entire length of the spinal cord and with contributing arteries, supplies a major portion of the anterior two-thirds of the spinal cord.

The posterior spinal arteries are four longitudinal running vessels, two on each side. One lies in front of the attachment of the dorsal nerve root, and the other or larger artery lies behind the attachment. These arteries are derived at the base of the brain, either directly from the vertebral artery or more often from a primary branch of the posterior inferior cerebellar artery, the largest branch of each vertebral artery. They supply the posterior one third of the spinal cord, i.e., the posterior gray horns and white columns.

Reinforcement of Arterial Supply

Contributing by anastomotic channels to the anterior and posterior spinal cord arteries are a succession of spinal radicular branches arising from local segmental arteries (derived from the aorta) of the vertebral, ascending cervical, posterior intercostal, spinal lumbar and lateral sacral arteries. Each spinal branch divides into an

anterior radicular and posterior radicular artery that approaches the spinal cord along the ventral and dorsal roots

Most of the anterior radicular arteries are small and terminate within the ventral nerve roots or in plexus of the pia around the cord. Frequently, one of these anterior radicular arteries is considerably larger than all the others and is termed the arteria radicularis magna, or the artery of Adamkiewicz. It arises from one of the intersegmental branches of the descending aorta at the lower thoracic or upper lumbar vertebral level usually on the left side (80%). This radicular artery may be responsible for the major blood supply of the lower two-thirds of the spinal cord in about 50% of the population.

The arterial supply to the spinal cord is a delicate system and is quite vulnerable to minor trauma and to vasoconstrictor drugs. Occlusion of the anterior spinal artery produces the anterior spinal artery syndrome denoted by lower limb paralysis without loss of posterior column sensation, i.e, touch, position, vibratory, and joint senses, or cauda equina syndrome denoted by sphincter disturbances.

Veins of the spinal cord

The veins of the spinal cord are situated in the pia mater. They are six in number and form longitudinal plexiform channels after

draining the parenchyma of the cord. In this plexus, there are (1) two median longitudinal veins, one anterior in the anterior fissure, and the other posterior at the posterior sulcus of the cord, and (2) four lateral longitudinal veins: one pair (posteriolateral) runs dorsal to the attachment of the nerve roots and the other pair ventral to the nerve roots (anterolateral). These veins communicate with the internal vertebral plexus, from which blood drains into the intervertebral veins. The intervertebral veins pass out through the intervertebral foramina to the segmental veins and to the external vertebral plexus.

Cerebrospinal fluid (CSF) [2]:

The term cerebrospinal fluid was first used in 1825 by French Physiologist F.Magendie. It is normally clear & colorless fluid that fills all the cavities and space around the central nervous system. It is isotonic with plasma. It is secreted mainly by choroid plexus of lateral ventricle and is reabsorbed by the arachnoid villi and granulations.

In a normal adult, cerebrospinal fluid is formed at a rate of 25 ml/hr or 600 ml/day. The replacement of total spinal fluid under ordinary normal physiological circumstances is every 6 hours. Cerebrospinal fluid is a complex solution containing an array of

molecules including electrolytes, proteins, glucose, neurotransmitters, neurotransmitter metabolites, cyclic nucleotides, amino acids, among many others. Cerebrospinal fluid is produced by ultra filtration of plasma in the choroid plexus and the cerebral/spinal capillaries and by oxidation of glucose, which produces water as a "by-product". The cerebrospinal fluid volume is approximately 100 to 160 ml in adult humans and it is produced at the rate of 20 to 25 ml/hr. Consequently, the entire cerebrospinal volume is replaced roughly every 6 hours.

Cerebrospinal fluid is removed by arachnoid villi present in the superior sagittal sinus and along many spinal nerve roots.

Baricity is defined as the ratio of the density (mass/volume) of the local anaesthetic solution divided by the density of cerebrospinal fluid, which averages 1.0003±0.0003 g/ml at 37°C. Solutions that have the same density as cerebrospinal fluid have a baricity of 1.0000 and are termed isobaric. Solutions that are denser than CSF are termed hyperbaric, whereas solutions that are less dense than CSF are termed hypobaric.

Baricity is important in determining local anesthetic spread and thus block height because gravity causes hyperbaric solutions to flow downward in CSF to the most dependent regions of the spinal column, whereas hypobaric solutions tend to rise in CSF. In contrast, gravity has no effect on the distribution of truly isobaric solutions. Thus, the anaesthesiologist can exert considerable influence on block height by choice of anaesthetic solution and proper patient positioning.

Characteristics of CSF

Specific gravity at 37°C 1.006 (1.003-1.009)

Volume 130-150 mL

Vol. in subarachnoid space 25 – 35 mL

Pressure 70-180 mm of water

Circulation

From the lateral ventricles cerebrospinal fluid passes through the foramina of Munro to the third ventricles, then through the aqueduct of sylvius to the fourth ventricle and then via foramen of Magendie to cisterna magna and via two foramen of Luschka into cisterna ponti. From the fourth ventricles it also passes into central

canal of spinal cord. From the central subarachnoid space, it reaches spinal subarachnoid space through the foramen magnum cerebrospinal fluid is absorbed into cranial venous sinuses through arachnoid villi.

Functions of CSF

1. It acts as cushion between the soft and delicate brain substance and rigid cranium.
2. Drainage of metabolites
3. Nutrition and oxygen supply to nerve cells to some extent.

PHYSIOLOGY OF CENTRAL NEURAXIAL BLOCKADE[4,5,6,7,8,9,10]

The well recognized physiological effects of subarachnoid block are often mistakenly termed as complications. It is imperative to make a clear distinction between the physiologic effects of an anaesthetic technique and complications that implies some harm to the patients.

The various factors[7,8] which affect the spread of local anaesthetics include,

Patient factors:

1. Age
2. Height
3. Position
4. Spinal column configuration
5. CSF volume

Technical factors:

1. Site of injection
2. Spread of injection
3. Direction of needle
4. Local anesthetic dose
5. Local anesthetic baricity
6. Local anesthetic volume

Factors not affecting the spread of local anaesthetic in the sub arachnoid space:

1. Weight of patient
2. Local anesthetic concentration
3. CSF composition
4. CSF circulation
5. Vasoconstrictors

Amount of drug

With greater amounts of drug there is an increase in the duration, height and intensity of spinal anaesthesia. There is an upper limit to the total amount of agent that may be used regardless of the volume and it is determined by the amount of that drug which may produce neurological damage.

.*Volume of solution*

If the amount of drug is maintained same, increasing the volume may increase the extent of anaesthesia. If the total volume is small the effect of volume augmentation is limited.

Site of injection

Selection of one or two spaces higher than usual L3-L4 interspace provides a higher level of anaesthesia when all other conditions are constant.

Rate of injection

This is perhaps the most important factor in determining the height of anaesthesia. With slow injections, the levels are low. Very rapid injections may cause anaesthesia to reach well into the thoracic area. Rate of injection 0.2ml/sec.

Barbottage

The term is derived from the French word 'barboter'- to puddle or mix. This is the technique of stirring up to increase turbulence, mixing of injected solution and increasing distribution in the sub arachnoid block. The to and fro movement agitates the injectate in the spinal fluid and mixes the agent more completely and carry the agent more extensively to higher levels.

Specific gravity, density and baricity

When hyperbaric solutions are used with patient supine in horizontal plane the anaesthetic will preferentially travel to the low points of sub arachnoid space i.e., below L3 into the lumbosacral concavity. Hyperbaric solutions travel to the most dependent part of the subarachnoid space when there are deviations of the patient's position from the horizontal. Isobaric solutions are considered not to spread with changes in position and the levels of anaesthesia are independent of positioning. The solution puddles near the site of injection.

Hypobaric solutions in contrast to hyperbaric solutions are not influenced by gravity and position of patient. They are administered while patient is in prone position.

Pharmacokinetics of spinal anaesthesia

There is a fall in the concentration soon following the injection of anaesthetic agent into the subarachnoid space. The reason being,

1. Dilution and mixing of CSF
2. Diffusion and distribution to neural tissues
3. Uptake and fixation by neural tissues
4. Vascular absorption and elimination
5. Through arachnoid villi

Initially, there is a rapid decrease in the concentration of drug, which occurs within 2-3 min soon after the injection of drug. This is due to mixing and dilution with CSF, which depends on the force or rate of injection of drug and amount or volume of fluid in the subarachnoid space.

The second phase of decrease in concentration is due to diffusion of agent in the spinal fluid by virtue of its molecular motion.

At the same time some of the agent is being absorbed into the nervous tissue.

This absorption occurs along a concentration gradient to 3 sites:

1. The nerve roots directly bathed by the anaesthetics.

2. Directly into the spinal cord surface by diffusion through the piamater.

3. Into the deeper parts of the spinal cord parenchyma through Virchow-Robin spaces.

Uptake of local anaesthetic from the spinal fluid and from the nerve fibres into the vascular compartment accounts for the third phase of slow decrease in total concentration of agent in the spinal fluid. The greater portion of the drug leaves the subarachnoid space through the venous drainage, while a small portion leaves through small lymphatic channels. Little or no breakdown of local anaesthetic agents occurs in the subarachnoid space or in the CSF.

The sequence of nerve modality block[9]

1. Vaso motor block – dilatation of skin vessels and increased cutaneous blood flow.

2. Temperature fibres – cold first and then warmth

3. Loss of temperature discrimination

4. Pain – pin prick fibres first

5. Loss of tactile sensation

6. Motor paralysis

7. Pressure sensation

8. Proprioception and vibratory sensation

The recovery, return of sensibility is in the reverse order. Sympathetic blockade is the major determinant of physiologic response to spinal anaesthesia. Indirect effects of spinal anaesthesia may be considered as a result of paralysis of these nerves.

Effect of Spinal Anaesthesia on Various Organs[10]

Cardiovascular System

Cardiovascular changes are the most important physiologic response to spinal anaesthesia. They are mediated by combined autonomic denervation and higher levels of neural blockade and uninhibited vagal activity.

Sympathetic Denervation

The level of sympathetic blockade determines the magnitude of cardiovascular responses to spinal anaesthesia. Higher the level of neural blockade the greater would be the changes in cardiac and circulatory parameters. In the presence of partial sympathetic blockade a reflex increase in sympathetic activity occurs in sympathetically intact areas. The result is vasoconstriction that tends to compensate for peripheral vasodilatation taking place in sympathetically denervated areas.

Arterial Circulation

Sympathetic denervation produces arteriolar vasodilatation, relaxation of vascular smooth muscles on the arterial side of circulation. As a result of this total peripheral vascular resistance

decreases about 15% to 18% in normal subjects in the presence of total sympathetic denervation provided the cardiac output and other determinants of blood pressure are kept normal.

Venous Circulation

Veins and venules with only few smooth muscles on their walls have no significant residual tone. Hence following pharmacological denervation, no significant change. They can vasodilate maximally. This is determined by intraluminal hydrostatic pressure.

Intraluminal hydrostatic pressure on the venous sides of the circulation depends on the gravity. If the denervated veins lie above the level of right atrium, it causes the blood flow back to the heart. Preload to the heart therefore depends on the position of the patient during spinal anaesthesia.

Heart Rate

Spinal Anaesthesia is characteristically associated with slowing of the heart rate. The degree of bradycardia as well as the frequency with which it occurs can be roughly correlated with the extent of sympathetic denervation.

Pronounced bradycardia is observed most frequently when cardiac output and arterial blood pressures have decreased significantly.

Cerebral Blood Flow

Cerebral blood flow is governed by two main factors. Mean arterial blood pressure and local resistance to blood flow in cerebral vessels. Spinal anaesthesia theoretically could influence cerebral blood flow altering either blood pressure or cerebrovascular resistance or both. Cerebrovascular auto regulatory mechanism maintains cerebral blood flow in humans at constant levels in the presence of wide fluctuations in mean arterial blood pressure.

Cerebral blood flow will become pressure dependent until the mean arterial pressure (MAP) falls below 55 mm Hg. Cerebrovascular auto regulation is independent of the sympathetic nervous system. Cerebral blood flow remains unaffected in normal persons even when mean arterial pressure decreases from 90 to 60 mm Hg during spinal anaesthesia.

The respiratory system

The phrenic nerve supplying the diaphragm arises from the anterior roots of C3-C5 and should not be encroached on in spinal analgesia, but phrenic paralysis can occur. Apnea may be due to medullary ischemia or due to toxic effects of the drug in extradural blocks. During spinal analgesia breathing becomes quiet and tranquil. This is not only due to motor blockade but also due to deafferentiation with reduction of sensory input to the respiratory centre.

Lowered arterial and venous tone also lessens the work of the heart and tends to relive any existing pulmonary congestion. The ventilation perfusion relationship during extradural block is not greatly altered and the effect on respiratory function is relatively small with no evidence of change in functional residual capacity or V/Q ratio. The pulmonary gas-exchange is preserved. Intercostal paralysis is compensated for by increased descent of the diaphragm, which is made easier by a lax abdomen

The gastrointestinal system

Pre-ganglionic sympathetic fibres from T5-Ll are inhibitory to the gut. There is no effect on oesophagus, the innervation of which is vagal. The small gut is contracted as sympathetic inhibitory impulses are removed, the vagus being all-powerful. The sphincters are relaxed and peristalsis is active although not more frequent. Pressure within the bowel lumen is increased. Handling of small bowel by the surgeon may cause it to dilate, as may the injection of atropine before the operation. Nausea and vomiting due to the hypotension may occur and usually comes on in waves lasting a minute or so and passes away spontaneously.

The Spleen

The spleen enlarges 2-3 times in high blocks when its sympathetic efferent fibres are paralyzed. Colonic blood supply and oxygen availability are increased in animals following spinal analgesia, perhaps an important factor in the prevention of anastamotic breakdown following gut resection.

The liver

The degree of hypotension, which compromises liver function, is not known. If the liver is diseased, a decrease in the mean arterial pressure affects the liver blood flow and also the metabolism of amide anaesthetics.

Endocrine system

Spinal block delays adrenal responses to injury and trauma, so there is no change in the levels of 17- hydroxy corticosteroids. Spinal block suppresses the hyperglycemic response to surgery and stress and so is useful in diabetic patients. The response to insulin is augmented, one should be aware of possibility of hypoglycaemia. Infused glucose through intravenous route is well utilized.

Genitourinary system

Sympathetic supply to kidney is from T11-L1 via the lower splanchnic nerve. Any effects on renal function are solely due to hypotension, renal blood flow is decreased but does not cease until blood pressure has fallen to about 80mm Hg. These changes are transient and disappear when blood pressure rises again. The penis is often engorged and flaccid due to paralysis of Nervi erigenti (S2-S3)

and this is also a positive sign of a successful block. Post spinal retention of urine may be moderately prolonged as S2-S3 contains small autonomic fibres and their paralysis lasts longer that of larger sensory and motor fibres. During prolonged blockade of lumbar and sacral segments, the bladder must be palpated so that catheterization can be employed when necessary. Spermatorrhoea is sometimes seen.

Uterus

The tone of uterus is not greatly altered after spinal analgesia in pregnancy. Blockade of nerves from T11 downwards results in painless labour. In late pregnancy, smaller doses of local anaesthetics are required because of decreased extradural space.

Body temperature

Vasodilatation favours heat loss, absence of sweating favours hyperpyrexia in hot environment, catecholamine secretion is depressed hence heat loss is produced by metabolism.

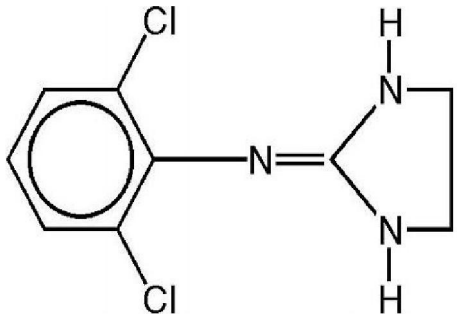
PHARMACOLOGY OF CLONIDINE[11,12,13,14,15,16,17]

Clonidine, an Imidazoline derivative, was synthesized in the early 1960s and was found to produce vasoconstriction which was mediated by alpha receptors.

CHEMISTRY

$C_9H_9N_3Cl_2.HCl$

2,6-Dichloro-N-2-imidazolidinylidenebenzaminehydrochloride.



PHARMACOLOGY

The α2-Adrenergic receptor

Clonidine is a partial agonist at alpha adrenoceptors both within the central nervous system and in the periphery. It is more specific for alpha 2-adrenoceptors than for alpha 1-adrenoceptors with a ratio of affinities at these sites of approximately 200:1. Within the central nervous system alpha 2-adrenoceptors are located both presynaptically on terminals of neurons which release a variety of

transmitters norepinephrine, epinephrine, serotonin and acetylcholine, and postsynaptically on nor-adrenergic neurons. It is likely that clonidine acts at all central alpha 2-receptors, stimulation of which is associated with decreased neuronal excitability and inhibition of membrane bound adenylate cyclase.

High concentrations of clonidine may stimulate central alpha1 adrenoceptors enhancing neuronal excitability. Stimulation of peripheral presynaptic a2-adrenoceptors on post ganglionic noradrenergic or cholinergic neurons by clonidine contributes to reduced saliva flow, reduced intestinal motor activity and gastric acid secretion, and bradycardia.

Endocrine and metabolic effects apparently mediated by alph2 adrenoceptor stimulation are, increased TSH and GH secretion, decreased ACTH and ADH secretion, and inhibition of glucose-stimulated insulin release. Clonidine inhibits insulin secretion from the pancreatic R cell possibly via an alpha 2 receptor. An alternative explanation is that this action is mediated via an Imidazoline receptor. The pressor effect of high doses of clonidine is due to peripheral vasoconstriction mediated by stimulation of postsynaptic alpha 1 and alpha 2 adrenoceptors on vascular smooth muscle.

Questions remain about whether the sympatho-inhibitory action of clonidine results solely from its a2-receptor agonism or whether part or all of its actions are mediated by Imidazoline receptors.

The Imidazoline receptor

Imidazoline receptors include three subtypes (I_1, I_2 and I_3), and are widely distributed in the body, including the CNS. Clonidine, as an imidazoline binds to these imidazoline receptors, in addition to its well-described binding to alpha2 receptors. Data suggest that imidazoline receptors make only a minor contribution to the ability of clonidine to inhibit norepinephrine release, while the main contribution to the action of clonidine is via α2-receptors.

PHARMACOLOGICAL ACTIONS

CARDIOVASCULAR ACTIONS

The major pharmacological effects of clonidine involve changes in blood pressure and heart rate, although the drug has a variety of other important actions. Intravenous infusions of clonidine cause an acute rise in blood pressure, apparently because of the

activation of post synaptic α2- receptors in vascular smooth muscle. Oral or intravenous administration of clonidine causes a dose-dependent fall in blood pressure and heart rate in both the supine and erect positions, with the orthostatic response being more prominent that are not seen in patient taking clonidine chronically.

The hypertensive response preceding the hypotensive effect following acute intravenous administration of clonidine, generally is not seen with oral administration. However, even after intravenous administration, the transient vasoconstriction is followed by a more prolonged hypotensive response that results from decreased sympathetic outflow from the CNS.

The blood pressure lowering effect appears to result, at least in part from activation of α2 receptors in the lower brainstem region.

ENDOCRINE AND METABOLIC EFFECTS

In patients with the usual low fasting plasma growth hormone (GH) concentrations, clonidine acutely increases plasma GH concentrations (mean 10-20 fold) and chronically may be associated with increases of variable magnitude in basal GH concentrations.

With high basal GH concentrations, clonidine acutely and chronically decreases HGH concentration.

Acute and chronic administration of clonidine reduces plasma ACTH and cortisol concentrations. There is no effect on the plasma concentrations of prolactin, FSH, or LH. Clonidine also causes a small rise in blood glucose and a fall in plasma insulin in normal persons. Both effects are inhibited by the peripheral a2-antagonist MK – 467.

The effects of clonidine on carbohydrate metabolism appears to be variable. Some studies suggest that clonidine does not affect carbohydrate metabolism in diabetic or non-diabetic hypertensive patients, although there has been a report of a diabetic patient in whom clonidine was associated with elevated fasting blood-glucose values, and increased insulin requirements were noted in a diabetic child treated with clonidine for tics. Conversely, clonidine was associated with severe hypoglycemia in children when used as a provocative test for growth hormone deficiency. Studies have shown that clonidine administration in animals and man causes slight

hyperglycemia, lipid mobilization and increase in growth hormone levels.

Clonidine induced defective insulin secretion and impaired glucose tolerance by selective stimulation of a-adrenergic pathways. This induction of hyperglycemia by clonidine was reversed by infusions of the a-adrenergic blocking agent phentolamine and in the presence of a-blockade; clonidine had no effect on plasma glucose.

Clonidine was reported to decrease glucose tolerance in maturity onset diabetics without any significant effect on glycemic control, and clonidine was also shown to favourably alter lipid profile. Clonidine appears to be promising in diabetic hypertensive patients, but more studies are warranted due to paucity of data on its lipid effects.

ACTIONS ON GASTROINTESTINAL TRACT

Clonidine may stimulate α2-adrenoceptors on enterocytes thus promoting fluid and electrolyte absorption and inhibiting anion secretion. It may also modify intestinal motility and rectal sphincter

tone. Because of these antidiarrhoeal properties, clonidine has been found to be of benefit in diabetic diarrhoea.

PHARMACOKINETICS

Clonidine is well absorbed after oral administration, and its bioavailability is nearly 100%, with peak concentrations in plasma and the maximal hypotensive effect being observed 1 to 3 hours after an oral dose. The elimination half-life of the drug ranges from 6 to 24 hours, with a mean of about 12 hours. Approximately half of the administered dose can be recovered unchanged in urine, and the half-life of the drug may increase with renal failure. There is good correlation between plasma concentrations of clonidine and its pharmacological effects. A transdermal delivery patch, an alternative to oral therapy permits continuous administration of clonidine. The drug is released at an approximately constant rate for a week, requiring 3 or 4 days to reach steady-state concentrations in plasma.

When the patch is removed, plasma concentration remain stable for about 8 hours and then decline gradually over a period of several days, this decrease in concentration is associated with a rise in blood pressure. Clonidine crosses the placenta and is distributed into breast milk.

ADVERSE EFFECTS

The major adverse effects of clonidine are dry mouth and sedation occurring in at least 50% of patients and may require drug discontinuation. However, they may diminish in intensity after several weeks of therapy. Sexual dysfunction may also occur. Constipation is also common. Marked bradycardia is observed in some patients. These and some of the other adverse effects of clonidine are related to dose, and their incidence may be lower with transdermal administration of clonidine.

Other adverse effects which have been reported include depression, anxiety, fatigue, nausea, anorexia, parotid pain, sleep disturbances, vivid dreams, impotence and loss of libido, urinary retention or incontinence, slight orthostatic hypotension, and dry, itching or burning sensation in the eye. Transient fluid retention may be responsible for a reduction in hypotensive effect during continued treatment.

About 15 to 20% of patients develop contact dermatitis, rashes and pruritus with the use of transdermal delivery systems. Less frequently, bradycardia, including sinus bradycardia with atrioventricular block, other ECG disturbances, heart failure, hallucinations, cramp, Raynaud's syndrome, gynaecomastia, and transient abnormalities in liver function tests has been reported. Symptoms of over dosage include transient hypertension or profound hypotension, bradycardia, sedation, miosis, respiratory depression, convulsions, and coma.

Sudden withdrawal of clonidine may produce rebound hypertension i.e., withdrawal reactions follow abrupt discontinuation of long-term therapy with clonidine in some hypertensive patients. No teratogenicity, mutagenicity or carcinogenicity have been demonstrated with clonidine.

CONTRAINDICATIONS

Disorders of cardiac pacemaker activity and conduction.

Sino-atrial node disease (Sick sinus syndrome)

Atrioventricular node disease.

THERAPEUTIC USES

1. In hypertension
2. Anxiety disorders
3. Glaucoma
4. Psychiatric disorders
5. Diarrhoea
6. Cardiac arrhythmias
7. Extrapyramidal disorders
8. Growth retardation
9. Menopausal disorders
10. Orthostatic hypotension
11. Migraine
12. Premedication
13. Phaeochromocytoma
14. Shivering
15. Spasticity
16. Cyclosporine associated nephrotoxicity
17. Post herpetic neuralgia

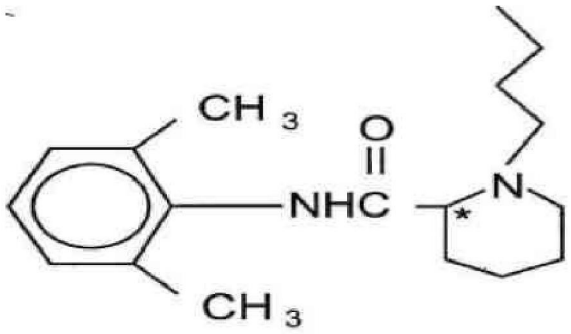
ROUTES OF ADMINISTRATION

1. Oral tablets
2. Transdermal patch
3. Intrathecal/epidural and intravenous injection
4. Intra Venous Regional Anesthesia
5. Plexus Block

PHARMACOLOGY OF BUPIVACAINE[15,16,17]

Bupivacaine, an amino amide local anaesthetic was first synthesized in Sweden by A.F Ekenstam and his colleagues in 1957. First report of its use was in 1963 by L.J Teluvio. It is one of the long acting local anaesthetic agents available, which is extensively used for intrathecal, extradural and peripheral nerve blocks. It is a white crystalline powder soluble in water

CHEMICAL STRUCTURE OF BUPIVACAINE



Bupivacaine has an IUPAC nomenclature of 1-butyl-n-(2,6-dimethylphenyl) piperidine-2-carboxamide.

Physiochemical properties[18]

Molecular formula	: $C_{18}H_{28}N_{2O}HCl$
Molecular weight	: 288.43 g/mol
Solubility in water	: 25mg/ml
pH of saturated solution	: 5.2
pKa	: 8.1
Specific gravity	: 1.021 at c37 °C
Melting point	: 247 - 258°C

Mechanism of action[19,20]

Mechanism of action of bupivacaine is similar to that of any other local anaesthetic. The primary action of local anaesthetics is on the cell membrane of the axons, on which it produces electrical stabilization. Bupivacaine prevents transmission of nerve impulses (conduction blockade) by inhibiting passage of sodium ions through ion-selective sodium channels in nerve membranes.

The sodium channel is a specific receptor for local anaesthetic molecules. The local anaesthetics block the nerve conduction by decreasing the entry of sodium ions during upstroke of action potential.

As the concentration of the local anaesthetic is increased, the rate of rise of action potential and maximum depolarisation decreases causing slowing of conduction. Finally local depolarization fails to reach the threshold potential and conduction block ensues.

The mechanism by which local anaesthetics block sodium conductance is as follows

1) Local anaesthetics in the cationic form act on the receptors within the sodium channels on cell membrane and block it. The local anaesthetics can reach the sodium channel either via the lipophilic pathway directly across the lipid membrane, or via the axoplasmic opening. This mechanism accounts for 90% of the nerve blocking effects of amide local anaesthetics.

2) The second mechanism of action is by membrane expansion. This is a nonspecific drug receptor interaction.

Other site of action targets

- Voltage dependent potassium ion channels
- Calcium ion currents (L-type most sensitive)
- G protein coupled receptors

Dosage depends on

Area to be anaesthetized

Number of nerve segments to be blocked

Individual tolerance

Technique of local anaesthesia

Vascularity of area

Bupivacaine is available in the following concentrations

0.25%. 0.5%and 1%

0.25% and 0.5% solution in isotonic saline

0.5% solution in 8% dextrose

ANESTHETIC POTENCY

Hydrophobicity appears to be a primary determinant of intrinsic anesthetic potency and Bupivacaine is highly hydrophobic, hence is very potent.

ONSET OF ACTION

The onset of conduction blockade is dependent on the dose or concentration of the local anesthetic. The onset of action of bupivacaine is between 4 – 6 minutes and maximum anaesthesia is obtained between 15 – 20 minutes.

DURATION OF BLOCK

The duration of anesthesia varies according to the type of block; the average duration of peridural block is about 3.5 – 5 hours, for nerve blocks, it is about 5 – 6 hours.

PHARMACOKINETICS

The rate of systemic absorption of local anaesthetics is dependent upon the total dose and concentration of drug administered, the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the anaesthetic solution. A dilute concentration of epinephrine (1:200,000 or 5 mcg/ml) usually reduces the rate of absorption and peak plasma concentration of bupivacaine, permitting the use of moderately larger total doses and sometimes prolonging the duration of action.

Plasma binding

In plasma, drug binds avidly with protein to the extent of 70 - 90%. The rank order of protein binding for this and its homologues is bupivacaine > mepivacaine > lidocaine. Conversely, the unbound active fraction is one seventh of lidocaine and one fifth of mepivacaine.

Absorption

The site of injection, dose and addition of a vasoconstrictor determine the systemic absorption of Bupivacaine .The maximum blood level of bupivacaine is related to the total dose of drug administered from any particular site. Absorption is faster in areas of high Vascularity.

Toxicity

The toxic plasma concentration is set at 4 - 5 µg/ml. maximum plasma concentration rarely approach toxic levels.

Distribution

The two-compartment model can describe this. The rapid distribution phase is believed to be related to uptake by rapid equilibrating tissue i.e., tissues that have high vascular perfusion. The slow distribution phase is mainly a function of distribution to slowly equilibrating tissue, biotransformation and excretion of the compound. More highly perfused organs show higher concentrations of the drug. Bupivacaine is rapidly excreted by lung tissue. Though skeletal muscle does not show any particular affinity for bupivacaine it is the largest reservoir of the drug

PHARMACODYNAMICS

Central Nervous System

Bupivacaine readily crosses the blood brain barrier causing central nervous system depression following higher doses. The initial symptoms involve feeling of light-headedness and dizziness followed by visual and auditory disturbances. Disorientation and drowsiness may occur. Objective signs are usually excitatory in nature, which includes shivering, muscular twitches and tremors, initially involving muscles of the face (perioral numbness) and part of extremities. At still higher doses cardiovascular or respiratory arrest may occur. Acidosis increases the risk of CNS toxicity from bupivacaine, since an elevation of PaCO2 enhances cerebral blood flow, so that more anesthetic is delivered rapidly to the brain

Autonomic nervous system

Bupivacaine does not inhibit the Noradrenalin uptake and hence has no sympathetic potentiating effect. Myelinated preganglionic B fibers have a faster conduction time and are more sensitive to action of Bupivacaine. When used for conduction blockade, all local anesthetics, particularly bupivacaine produces higher incidence of sensory than motor fibers

Cardiovascular System

The primary cardiac electrophysiological effect of a local anaesthetic is a decrease in the maximum rate of depolarization in Purkinje fibers and ventricular muscle. This action by bupivacaine is far greater compared to lignocaine and also, the rate of recovery of block is slower with bupivacaine. The resulting slowed conduction of the cardiac action potential manifest on the electrocardiogram as prolongation of the P-R and QRS intervals and reentry ventricular cardiac dysrhythmias. The R enantiomer of bupivacaine is more toxic than the S enantiomer. Bupivacaine reduces the cardiac contractility by blocking the calcium transport. Low concentration of bupivacaine produces vasoconstriction whereas high doses cause vasodilatation.

Respiratory System

Respiratory depression may be caused if excessive plasma level is reached which in turn results in depression of medullary receptor center. Respiratory depression may be also caused by paralysis of respiratory muscles of diaphragm as may occur in high spinal or total spinal anesthesia

Biotransformation and Excretion

Bupivacaine undergoes enzymatic degradation primarily in the liver. The excretion occurs primarily via the kidney. Renal perfusion and factors affecting urinary pH affect urinary excretion. Less than 5% of bupivacaine is excreted via the kidney unchanged through urine. The major portion of injected agent appears in urine in the form of 2,6 pipecolyoxylidine (ppx) which is a n-dealkylated metabolite of bupivacaine. Renal clearance of the drug is related inversely to its protein binding capacity and pH of urine.

Adverse Effects

Adverse effects are encountered in clinical practice mostly due to overdose, inadvertent intravascular injection or slow metabolic degradation.

Central nervous system

It is characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurring of vision or tremors, followed by drowsiness, convulsions, unconsciousness and respiratory arrest.

Cardiovascular system

Myocardial depression, hypotension, arrhythmia, ventricular type conduction defect, SA node depression and cardiac arrest

Allergic reactions

Urticaria

Bronchospasm

Hypotension

Other - nausea, vomiting, chills, constriction of pupil and tinnitus

REVIEW OF LITERATURE

Prachee sachan et al[41] in 2014 conducted a randomised contoled study in caesarean section by administering intrathecal clonidine with hyperbaric bupivacaine as a mixture and sequential. They compared the block characteristics, intraoperative haemodynamics and postoperative pain relief. They randomly allocated 60 full-term parturients scheduled for elective caesarean sections were divided into two groups on the basis of technique of intrathecal drug administration. Group M received mixture of clonidine (75 mcg) and hyperbaric bupivacaine 0.5% (10 mg) intrathecally, whereas Group B received clonidine (75 mcg) followed by hyperbaric bupivacaine 0.5% (10 mg) through separate syringes. They observed duration of analgesia was significantly longer in Group B (474.33 ± 20.79 min) in which the drug was given sequentially than in Group M (337 ± 18.22 min). Furthermore, the time to achieve highest sensory block and complete motor block was significantly less in Group B without any major haemodynamic instability and adverse neonatal outcome. Therefore they concluded that when clonidine and hyperbaric bupivacaine were administered

in a sequential manner, block characteristics improved significantly compared to the administration of the mixture of the two drugs.

Ranju singh et al[40] in 2013 conducted a study to evaluate the effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain after lower segment caesarean section. : A total of 105 parturients carrying a singleton fetus at term, scheduled to undergo elective LSCS under spinal anaesthesia were randomized in a double blind fashion to one of the three groups. Group BF (n=35) received 2ml of 0.5% hyperbaric bupivacaine+25 µg fentanyl, Group BC50 (n=35) received 2 ml of 0.5% hyperbaric bupivacaine+50 µg clonidine, Group BC75 (n=35) received 2 ml of 0.5% hyperbaric bupivacaine +75 µg clonidine. They observed that the duration of postoperative analgesia was 184.73±68.64 min in group BF, 360.71±86.51 min in group BC50 and 760.50±284.03 min in group BC75,with P<0.001. Neonatal outcome was similar in all the three groups. They concluded addition of 75 µg clonidine to hyperbaric bupivacaine in spinal anesthesia for LSCS significantly prolongs the duration of postoperative analgesia without any increase in maternal side effects. There was no difference in neonatal outcome.

Agreta Gecaj-Gashi, et al[24] conducted a prospective, double-blinded study in 2012 to evaluate the effects of clonidine in co-administration with bupivacaine in spinal anesthesia, regarding the onset and regression of sensory and motor block, postoperative analgesia and possible side effects. They randomly selected 66 male patients (age 35 to 70),of ASA class I–II posted for transurethral surgical procedures.They randomly allocated two groups of 33 patients each, group B received 0.5% isobaric bupivacaine 7.5 mg intrathecally and group BC received bupivacaine 7.5 mg and clonidine 25 μg intrathecally.They observed the mean time of achievement of motor block (Bromage 3) and sensory block at level T9 was significantly shorter in the group BC than with group B (p = 0.002, p = 0.000, respectively). The motor block regression time was not significantly different between the two groups (p = 0.237). The postoperative analgesia requirement was significantly longer in BC group than with B group (p = 0.000). No neurological deficit, sedation or other significant adverse effects were recorded. They concluded intrathecal administration of clonidine with bupivacaine improves the duration and quality of spinal anaesthesia. It also provides longer duration of postoperative analgesia, without any significant side effects.

S.desai et al[27] in 2010 conducted a randomised controlled trial of hyperbaric bupivacaine with opioids, injected as either a mixture or sequentially, for spinal anaesthesia for caesarean section. Mixing these drugs may alter the density of the hyperbaric solution, affecting the spread of local anaesthetic and opioid. Forty-eight women having elective caesarean section under spinal anaesthesia were recruited to this double-blind, randomised trial. Group M (n=24) received 2 ml of 0.5% hyperbaric bupivacaine plus morphine 100 µg plus fentanyl 15 µg, mixed in a syringe prior to administration. Group S (n=24) received 2 ml of 0.5% bupivacaine through one syringe, followed by morphine 100 µg plus fentanyl 15 µg through a separate syringe. Block characteristics, postoperative pain scores and morphine use were noted. The patients in Group M had higher levels of sensory block to than those in Group S (median T2 versus T3)(P=0.003). There was no difference between groups in the incidence of hypotension, need for vasopressor or any other side-effects. Morphine consumption was significantly higher in group M (13.3±11.2 versus 6.2±7.2 mg, P=0.015). They concluded mixing of fentanyl and morphine with hyperbaric bupivacaine results in a higher level of sensory block than sequential administration of

bupivacaine then opioid and may be associated with higher postoperative opioid requirement.

Imbelloni LE et al[29] in 2009 conducted an experimental study to determine the density of local anaesthetic solutions, with and without glucose, and the combination of the local anesthetic with adjuvants at 20° C, 25° C, and 37° C. The density (g/mL) was determined by using a DMA 450 densimeter with a sensitivity of ± 0.00001 g/mL . The densities, and variations, according to the temperature were obtained for all local anaesthetics and their combination with opioids at 20ºC, 25°C, and 37°C. The solution is hyperbaric if its density exceeds 1.00099, hypobaric when its density is lower than 1.00019, and isobaric when its density is greater than 1.00019 and lower than 1.00099. The densities of both local anaesthetics and adjuvants decrease with the increase in temperature. At 37° C, all glucose- containing solutions are hyperbaric. In the absence of glucose, all solutions are hypobaric. At 37°C, morphine, fentanyl, sufentanil, and clonidine are hypobaric. They concluded the densities of local anaesthetics and adjuvants decrease with the increase in temperature and increase when glucose is added.

Patricia M. Lavand'homme et al[26] conduted a study in 2008 to evaluate the postoperative antihyperalgesic effect of intrathecal clonidine after caesarean delivery. Ninety six parturients undergoing elective cesarean delivery were randomly allocated to Group BS (receive intrathecal bupivacaine-sufentanil) Group BSC (bupivacaine-sufentanil-clonidine 75 mcg) and GroupBC (bupivacaine-clonidine 150 mcg) . The primary outcome was the extent and the incidence of periincisional punctate mechanical hyperalgesia as assessed by response to application of a von Frey filament at 24 and 48 h after cesarean delivery. They observed Group (BC) had a significantly reduced area of periincisional hyperalgesia at 48 h (1.0 (1.0 – 3.3) cm2 versus Group BS 9.5 (5.0–14.0) cm2 versus Group BSC 5.0 (2.5–12.3) cm2 (P = 0.02 with the BS group). The incidence of hyperalgesia at 48 h was also lower in the BC group: 16% versus 41% in the BS group versus 34% in the BSC group (P = 0.03 with BS group). Postoperative morphine consumption, pain scores did not differ among groups. They concluded Intrathecal clonidine 150 mcg combined with bupivacaine had a postoperative antihyperalgesic effect expressed as a significant reduction in periincisional punctate mechanical hyperalgesia at 48 hr after elective cesarean section compared with intrathecal

bupivacaine-sufentanil and intrathecal clonidine 75 mcg-bupivacaine-sufentanil.

B.S.Sethi et al[33] conducted a study in 2007 to evaluate efficacy of analgesic effects of low dose intrathecal clonidine as adjuvant to bupivacaine. Study conducted in Sixty adult patients of ASA grade I and II, posted for gynaecological surgery under spinal anaesthesia were randomly divided into two groups. Clonidine group received clonidine1µg/kg with12.5mg0.5% bupivacaine (The maximum dose of clonidine used was70µg) and the Control group received an identical volume of saline mixed with 12.5mg 0.5%bupivacaine. The mean time from injection to two segment regression was longer in the clonidine group than in control group($P<0.001$). The duration of motor blockade was longer in clonidine group ($P<0.05$) than control group. There was a significant difference ($P<0.001$) in the mean duration of analgesia between the two groups, the recordings being,614min (480–1140min) in the clonidine group as against 223min (150- 300 min) in the control group.The rescue analgesia was required earlier in the Control group (mean223min) than clonidine group (mean614min).The patients in the clonidine group had a significant fall in heart rate and mean arterial pressure and were more sedated than those in control group, however, no therapeutic

interventions needed. They concluded that addition of clonidine to bupivacaine in the dose of 1µg/kg significantly increases the duration of spinal analgesia as compared to bupivacaine alone with clinically insignificant influence on haemodynamic parameters and level of sedation.

Van tuijl et al[30] in2006 conducted a randomized control trial to investigate the effect of the addition of clonidine (75 mg) to hyperbaric bupivacaine on postoperative morphine consumption after Caesarean section. A group of 106 women received spinal anaesthesia using either bupivacaine 0.5% (2.2 ml) heavy with 0.5 ml normal saline 0.9% (B) or bupivacaine 0.5% (2.2 ml) heavy with clonidine (75 mcg) in 0.5 ml normal saline 0.9% (BC).They observed the mean time to the first analgesic request in the BC group was 129 (SD 13.8) min, compared with 55 (14.2) min in the B group. They concluded the addition of clonidine (75 mcg) to hyperbaric bupivacaine prolongs duration of spinal anaesthesia after Caesarean section and improves early analgesia, but does not reduce postoperative morphine consumption during the first 24 hour.

Neves JF et al[39] conducted a study in 2006 to evaluate the addition of 15 to 30 µg of clonidine to 0.5% hyperbaric bupivacaine (12.5 mg) with morphine(100 µg) in spinal anesthesia for caesarean sections to improve the quality of postoperative analgesia,they randomly allocated sixty patients into three groups.Group BM received 0.5% hyperbaric bupivacaine 12.5mg and morphine 100mcg ,Group BM15 – 0.5% hyperbaric bupivacaine (12.5 mg), morphine (100 µg), and clonidine (15 µg), and Group BM30 – 0.5% hyperbaric bupivacaine (12.5 mg), morphine (100 µg),and clonidine (30 µg), administered separately. Intra operatively the use of ephedrine and the newborn's Apgar score were recorded. In the postoperative period, the pain was evaluated in the 12^{th} hr by the VAS score. They observed the use of ephedrine and the evaluation by the Apgar score did not show statistically significant differences among the different groups. The duration of post operative analgesia was increased in those received clonidine. So they concluded that the addition of clonidine to 0.5% hyperbaric bupivacaine (12.5 mg) with morphine (100 µg)in spinal anaesthesia for caesarean section improved the quality of postoperative analgesia without increasing the incidence of side effects.

Kaabachi O et al[32] conducted a prospective randomised study in 2002 to evaluate the effect of intrathecal clonidine in children . 45 children, 6 to 15 years old, were randomised in two groups; receiving either 0.5% hyperbaric bupivacaine or 0.5% hyperbaric bupivacaine added to clonidine 2 $\mu g \cdot kg^{-1}$. They assessed quality and duration of motor and sensory blocks and side effects of clonidine such as hypotension, bradycardia and sedation were noted. They obseved Clonidine was associated with prolongation of motor block, 190 ± 42 min vs 150 ± 35 min ($p < 0.01$), but the difference was not significant. Postoperative analgesia was longer in clonidine group, 490 ± 35 min vs 200 ± 50 min (mean ± SD), $p < 0.001$. Clonidine was associated with higher incidence of hypotension and bradycardia .They concluded that intrathecal clonidine 2 $\mu g \cdot kg^{-1}$ is associated with longer duration of postoperative analgesia but with moderate side effects such as hypotension, bradycardia.

Fonseca NM et al[42] in 2001 conducted a study to evaluate the effects of combined clonidine and 0.5% hyperbaric bupivacaine on spinal anaesthesia. Thirty ASA I or II patients of both genders, aged between 16 and 57 years and scheduled to undergo inguinal hernia repair were randomly allocated into three groups. Group I received bupivacaine 15 mg plus150 µg clonidine, Group II received

bupivacaine 15 mg and 75 µg clonidine + 0.5 ml distilled water and Group III received bupivacaine 15 mg plus 1 ml of distilled water. The following parameters were evaluated: sensory block level at 5, 20 and 30 minutes, time for two segment regression, sedation scores , motor block by a modified Bromage scale, postoperative pain and analgesics requirement. They observed maximum sensory level were similar for all groups. Duration of sensory and motor block were longer for Group I. There were no difference in sedation and hemodynamic parameters between groups. Group I had a prolonged analgesia as compared to other groups. They concluded that clonidine has not changed cephalad spread and hemodynamic effects of spinal anaesthesia with hyperbaric bupivacaine. It was however effective in improving analgesia observed until the fourth hour after the blockade, as well as in prolonging anaesthesia duration, being therefore useful as a co adjuvant of spinal blocks with hyperbaric bupivacaine.

Dan Benhamou et al[22] conducted a multi center trial in1998 in Seventy eight pregnant women at term, scheduled for elective caesarean section, to compare the analgesic efficacy and side effect profile of hyperbaric bupivacaine alone (Group B) or bupivacaine combined with clonidine (Group BC) or with clonidine and fentany1 (Group BCF). Group B received hyperbaric bupivacaine

and 1 ml of saline, Group BC received hyperbaric bupivacaine with clonidine 75 µg (0.5 ml) and saline (0.5 ml), and in Group BCF received bupivacaine with fentanyl (12.5 µg in 0.5 ml) added to clonidine (75 µg). The dose of bupivacaine was similar in all groups (0.06 mg/cm of body height). They observed clonidine increased the spread of the sensory block and decreased pain and analgesic supplementation intra operatively. This improved analgesia was best with the clonidine fentanyl combination (Group BC versus Group BCF; $P < 0.05$). Postoperative analgesia was prolonged only in Group BCF (215 ± 79 min versus 137 + 35 and 183 ± 80 min for Group BCF versus Groups B and BC; $P < 0.05$). Blood pressure and heart rate changes were not significantly different among groups, except sedation and pruritis which were significant in Group BCF. Apgar scores and umbilical artery blood pH were not different among groups. They concluded adding a small dose of intrathecal clonidine (75mcg) to bupivacaine increases the quality of intra operative analgesia without adverse neonatal outcome. The combination of clonidine and fentanyl further improved analgesia with moderately increased sedation and pruritis.

Heo GJ et al[35] conducted a study in 1997 to evaluate effect of intrathecal clonidine in hyperbaric bupivacaine spinal anesthesia. They randomly allocated thirty patients who were scheduled for lower limb or urologic operation and were divided into 2 groups: Group A (hyperbaric bupivacaine 13 mg, 2.6 ml + 0.9%saline 1 ml), Group B (hyperbaric bupivacaine 13 mg, 2.6 ml + clonidine 150mcg, 1 ml). They used standardized techniques and injected above drugs to group A and B intrathecally for spinal anesthesia. They observed the onset and the duration of spinal anaesthesia along with hemodynamic changes (blood pressure and heart rate). They observed no significant differences in the onset of spinal anaesthesia and hemodynamic changes between two groups. The time taken to recover from the nerve block was more prolonged in the group B (touch 225, pain 262, foot dorsiflexion 271, knee flexion 290 minutes) than group A (touch 154, pain 188, foot dorsiflexion 198, knee flexion 216 minutes). No significant differences in sedation, dry mouth and other side effects between the two groups. They concluded that Intrathecal clonidine 150mcg prolong the duration of hyperbaric 0.5% bupivacaine spinal anesthesia without neurotoxicity or dangerous hemodynamic

instability. Therefore, clonidine can be used as an effective adjuvant to hyperbaric bupivacaine in spinal anaesthesia.

Michael G Richardson et al[43] in 1996 conducted a study to determine the exact density of human cerebrospinal fluid and determine whether CSF density altered by pregnancy.density measurements accurate to 0.00001 g/ml were made at 37℃, using a mechanical oscillation resonance frequency density meter. CSF samples were obtained from 44 patients during spinal anaesthesia. Five groups were studied : men and premenopausal, postmenopausal, term pregnant and postpartum women. They observed mean CSF densities in men (1.00064±0.00012 g/ml), postmenopausal women (1.00070±0.00018 g/ml) and non pregnant premenopausal (1.00049±0.00004 g/ml) were significantly greater than in term pregnant (1.00030±0.00004 g/ml) and postpartum (1.0004±0.00005 g/ml) women. Cerebrospinal fluid density did not correlate with age.

Therefore they concluded mean CSF density varies in different patient subpopulations. Pregnancy and the immediate postpartum period are associated with the lowest CSF densities. In addition, the cutoff values defining hypobaricity(mean CSF desnity minus three standard deviations) are greater than previously reported. Accurate

CSF density values should be used when considering baricity as a mechanism for clinical observations of dextrose –free intrathecal local anesthetics and opioids. Gestational status also should be considered.

Gray et al[36] in 1986 investigated possible differences in the duration of postoperative analgesia and the incidence of respiratory depression after the intrathecal injection in the lumbar area of 10 mcg/kg morphine in hypobaric and hyperbaric solution for relief of post thoracotomy pain. Twenty-nine patients received morphine plus dextrose (hyperbaric) and 21 received morphine in preservative-free normal saline. They observed the duration of analgesia was longer with the morphine in the normal saline group than in the hyperbaric group ($P < 0.04$). They concluded morphine in normal saline mixtures produce greater duration of analgesia than morphine plus dextrose.

MATERIALS AND METHODS

After getting approval from the institutional ethical committee,the study was conducted in sixty parturients undergoing elective caesarean section under spinal anaesthesia. The patients were randomly allocated into two groups of 30 each by sealed envelope technique.

Inclusion criteria

- ASA grade1&2
- Single live fetus
- Uncomplicated pregnancy

Exclusion criteria

- Patient refusal
- Contraindication to subarachnoid block
- Multiple pregnancy
- Intrauterine death
- Known fetal anomaly
- Severe pregnancy induced hypertension
- Patient on cardiovascular medications
- Hypersensitivity to clonidine and local anaesthetis

All patients were thoroughly examined preoperatively. informed written consent obtained and the procedure was explained. they were allocated into following groups.

Group M: 10mg of 0.5%hyperbaric bupivacaine plus clonidine75microgram as a mixture in single syringe.

Group B: clonidine 75 microgram followed by hyperbaric bupivacaine 10mg in different syringes.

For our study, the drugs used were sourced from same company to avoid manufacturer's difference. hyperbaric bupivacaine used was HEAVY ANAWIN and clonidine used was CLONEON manufactured by neon laboratories.

Patients were kept fasting overnight and oral ranitidine 150 mg at night and on the morning prior to surgery were given. The patients were familiarised with concept of visual analogue scale (VAS) for pain assessment with o=no pain and 10= worst pain.

In the operating room, monitor for heart rate (HR),non invasive blood pressure, electrocardiography and oxygen saturation (SpO2) was connected and baseline parameters were recorded. after establishing 18 gauge venous cannula, patients were preloaded with 15 ml/kg of lactated ringer solution 15-20 min before spinal block. Under all aseptic precautions subarachnoid block was administered with 23 G Quincke spinal needle through midline approach in sitting position. Intrathecal drug was injected in L3-L4 inter space over 30 seconds (including the time for change of syringe in sequential administration). After the block was performed, the patients were made supine with 15-20 degree left displacement of uterus until delivery of baby by keeping wedge. Fluid therapy was maintained with ringer lactate 10 ml/kg/hr.

HAEMODYNAMIC PARAMETERS

Heart rate, systolic arterial pressure (SAP), diastolic pressure (DAP) were monitored every 2 minutes for the first 20 minutes and then every 5 minute subsequently until 75 minutes or until completion of surgery.

Hypotension (decrease in systolic pressure below 90 mmHg or fall in blood pressure >20% of baseline values) was treated with a rapid infusion of crystalloids 200 ml and a bolus of injection ephedrine 5mg intravenous was administered if hypotension persisted. Bradycardia heart rate <50 beats/minute was treated with injection atropine 10mcg/kg intravenously.

SENSORY AND MOTOR BLOCK

Sensory block was assessed by loss of pinprick sensation to 23G hypodermic needle in the midclavicular line bilaterally.

Onset of sensory blockade: is defined as time taken from the completion of the injection of study drug till the patient does not feel the pin prick at T10 level.

Time taken for maximum sensory blockade: is defined as the time taken from the completion of the injection of the study drug to the maximum sensory blockade attained. Sensory level was tested every 2 minutes until the highest sensory level (maximum block height) had stabilized for four consecutive tests.

Furthermore level was tested every 30 minutes until regression from highest level to T10 dermatome was noted.

MOTOR BLOCK

Onset of motor block: is defined as the time taken from the completion of injection of study drug till patient develops Bromage score2.

Time to achieve complete motor block: is defined as the time taken from the completion of injection of study drug till patient unable to move legs and feet.

Duration of motor blockade: is defined as the time taken from the time of injection till the patient attains complete motor recovery.

Degree of motor block was assessed by Bromage scale as follows

1 : Free movement of legs and feet

2 : Just able to flex knees with free movement of feet

3 : Unable to flex knees with free movement of feet

4 : Unable to move legs and feet

Motor block was assessed at the same interval as sensory block. Onset of motor block was assessed by time to reach bromage score2. Time to achieve complete motor block (bromage4) and its regression to bromage 1 was noted.

RESPIRATION

Respiratory depression was defined as rate <10breath/minute or Spo2 <92%. Oxygen was then supplemented through O2 mask 4L/minute.

SEDATION

Sedation score assessed same interval as sensory block until 2 hr postoperatively by Ramsay sedation score (RSS) as:

Level 1 - awake, anxious, agitated, restlessness

Level 2 – awake, tranquil, co-operative

Level 3 – responds to commands

Level 4 – asleep, brisk response to stimuli

Level 5 – asleep, sluggish response to stimuli

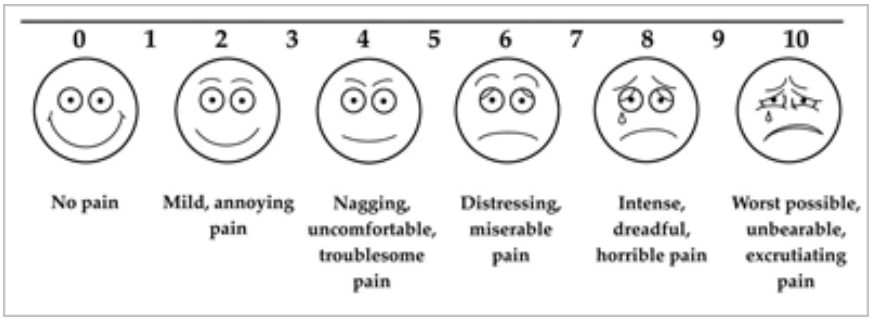
Level 6 – asleep, no response to stimuli

ANALGESIA

Duration of analgesia: is defined as the time taken from the completion of the injection of the study drug till the patient requests for rescue analgesic in the post operative period

Intra operative and post operative pain was checked and expressed as VAS, whenever the parturients complained of discomfort or pain. Duration of analgesia was defined as time of intrathecal administration to VAS >3. If VAS >3 then rescue analgesia in the form of intravenous diclofenac sodium 75 mg was given.

VISUAL ANALOGUE SCALE



Patients complaining of nausea or vomiting were given injection ondansetron 0.15mg/kg IV. Any complaint of dry mouth was noted. Newborns APGAR scores were determined by a paediatrician not otherwise involved in the study at 1, 5, and 10th minute.

Post-operatively any incidence of bradycardia, hypotension, nausea, vomiting was noted and treated accordingly. They were asked about the presence of headache (PDPH), back pain, numbness and tingling sensation in the lower extremities.

STATISTICAL ANALYSIS:

The information collected regarding all the selected cases were recorded in a master chart. Data entry was done using SPSS 21 for Windows. Descriptive statistics like percentages, mean with standard deviation and 95% confidence interval were used.

Independent t test was used to find the significance of difference between the two means and a P value of less than 0.05 was considered statistically significant

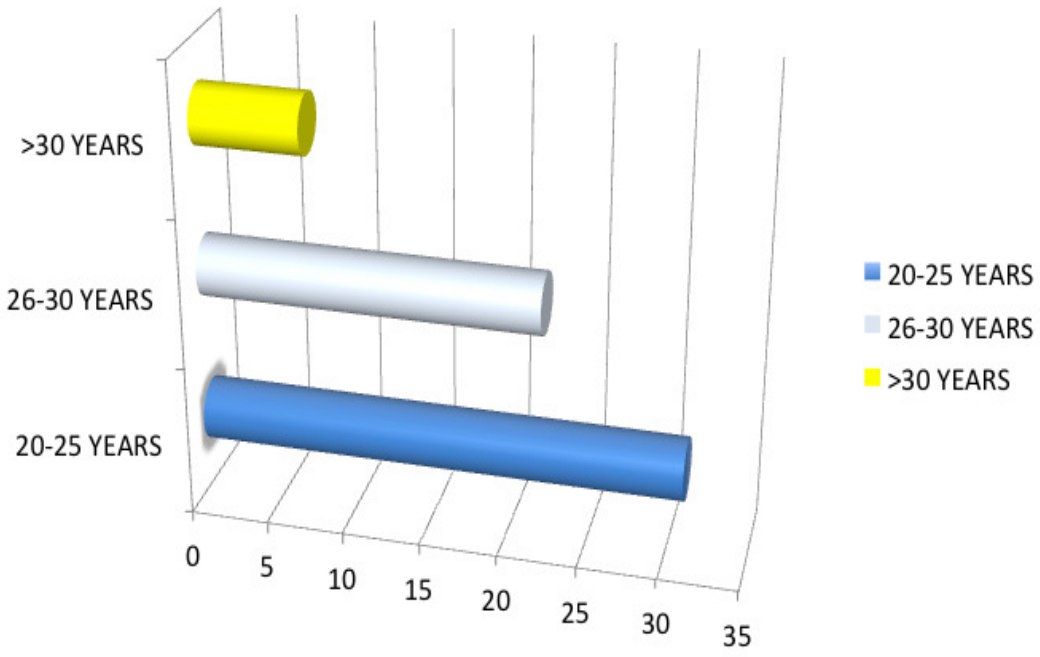
OBSERVATION AND RESULTS

All 60 patients in two groups completed the study without any exclusion. We did inter group analysis and the results were as followed. Of the 60 patients 30 belongs to Group M [mixture of clonidine75mcg and hyperbaric bupivacaine 0.5%(10 mg)] and other 30 categorized as Group B [clonidine 75 mcg followed by hyperbaric bupivacaine 0.5%(10 mg)]. Data were presented as maximum, minimum, mean, standard deviation. The probability value ‘ p’ of less than 0.05 was considered as statistically significant.

Table 1: Demographic profile of the patients

Variables	Group		P value
	Group M	Group B	
Age (years)	26.20±3.31	25.93±3.03	0.747
Weight (kgs)	59.27±2.97	59.87±2.98	0.438
Height (cms)	156.47±4.70	160.73±18.66	0.230
Duration of surgery (min)	79.33±6.98	80.30±1.84	0.466

The above table shows the demographic data in terms of age, height, weight and duration of surgery and they are comparable in both groups. They are found to be statistically insignificant.



The above figure shows the age distribution of the patients and more than half of the patients, 31(51.6%) of the patients belong to the age group of 20-25 years.

Table 2: Duration of surgery

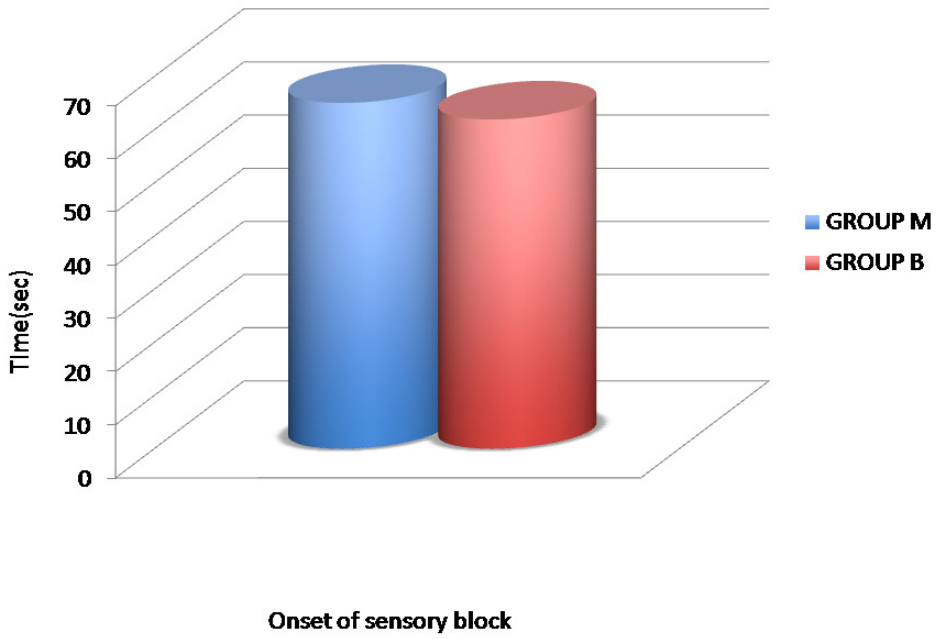
	Duration of surgery (min)	
	Group M	Group B
Mean	79.33	80.30
SD	6.98	1.84
Maximum	86	86
Minimum	65	78

Table 2 shows the mean duration of surgery between the Group M and Group B, and it is found to be 79.33±6.98 min and 80.30±1.84 min respectively.

Table 3: Onset of sensory block

	Onset of sensory block (sec)	
	Group M	Group B
Mean	65.03	61.93
SD	10.38	2.21
Maximum	90	65
Minimum	40	60
	P value 0.115	

Table 3 shows the onset of sensory block between the Group M and Group B, and it is found to be 65.03±10.38 and 61.93±2.21 respectively. It is statistically insignificant .(p value 0.115).

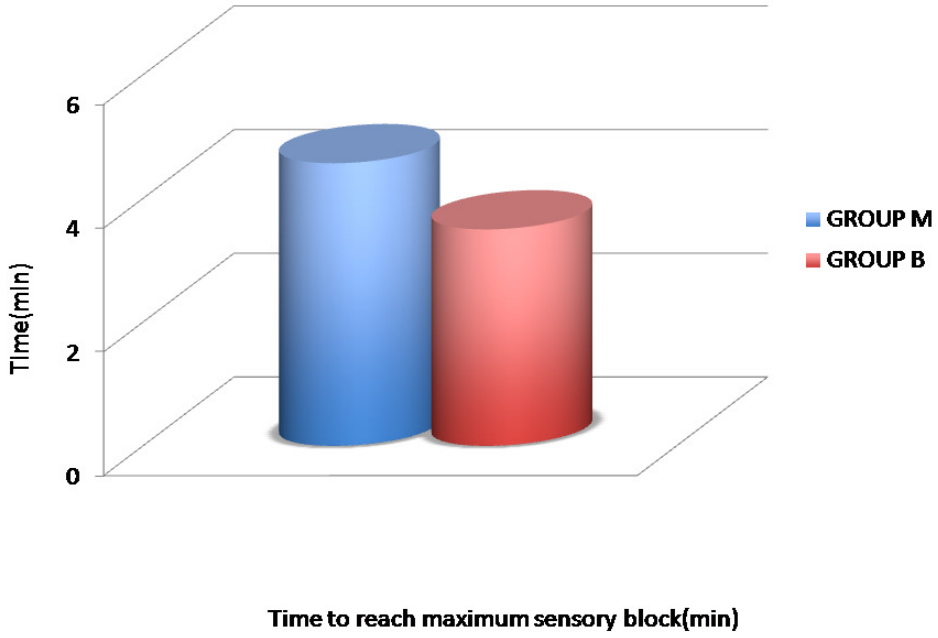


This graph shows the onset of sensory block between the GroupM and Group B

Table 4: Time to reach maximum height of sensory block

	Time to reach maximum height of sensory block (min)	
	Group M	Group B
Mean	4.57	3.50
SD	1.19	0.97
Maximum	7	5
Minimum	2	2
P Value 0.000		

Table 4 shows the time to reach the maximum height of sensory block and it is found to be maximum of 7 minutes and minimum of 2 minutes in group M with a mean of 4.57 minutes and among group B, it is found to have a maximum of 5 minutes and a minimum of 2 minutes, with a mean of 3.50 minutes. Mean time to reach maximal cephalad-sensory block height was significantly less in Group B (3.50±0.97 min) than in Group M (4.57±1.94 min) with p value of 0.000.

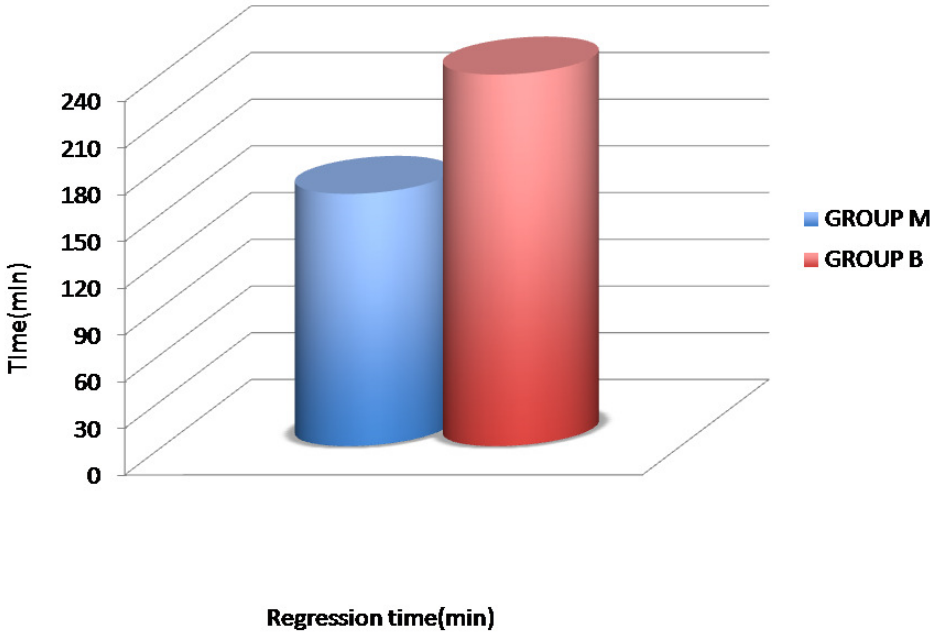


This graph shows the time to reach the maximum height of sensory block between the Group M and Group B

Table 5: Regression time to T 10

	Regression time (min)	
	Group M	Group B
Mean	162.03	238.67
SD	11.62	27.90
Maximum	188	262
Minimum	148	163
P Value 0.000		

The above table shows the regression time between the group M and group B and it is found to have an average of 162.03 minutes in group M and 238.67 minutes in group B with SD of 11.62 and 27.90 minutes respectively. Significant prolongation of sensory block in group B (p value 0.000).

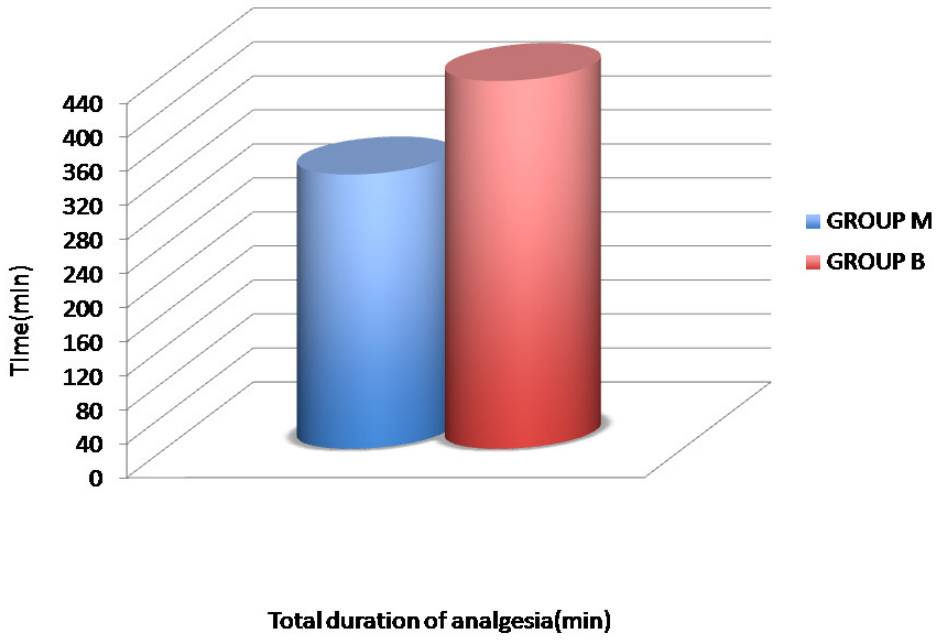


This graph shows the regression time to T10 between the Group M and Group B

Table 6: Total duration analgesia

	Total duration of analgesia (min)	
	Group M	Group B
Mean	322.53	432.60
SD	23.24	64.65
Maximum	360	500
Minimum	290	315
P Value 0.000		

The above table shows the total duration of analgesia between the group M and group B and it is found to have an average of 322.53 minutes in group M and 432.60 minutes in group B with SD of 23.24 and 64.65 minutes respectively. The total duration of analgesia lasted significantly longer in Group B (432.60±64.65 min) as compared to Group M (322.53±23.24 min) (P=0.000)

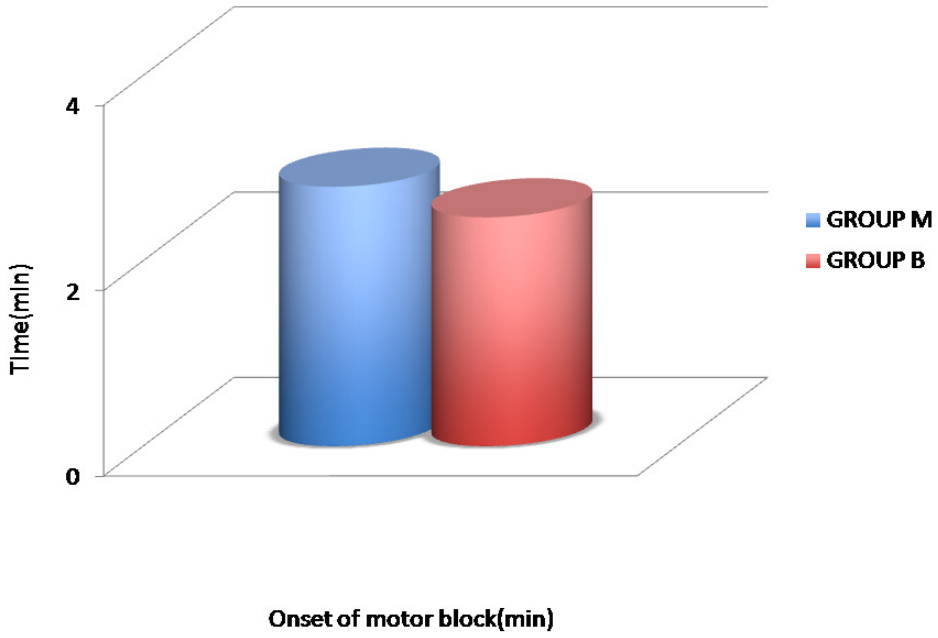


This graph shows the total duration of analgesia between the Group M and Group B

Table 7: Onset of motor block

	Onset of motor block (min)	
	Group M	Group B
Mean	2.80	2.47
SD	1.06	0.77
Maximum	4	4
Minimum	1	1
P Value 0.171		

Table 7 shows the onset of motor block and it is found to be maximum of 4 minutes and minimum of 1 minute in group M with a mean of 2.80 minutes and among group B, it is found to have a maximum of 4 minutes and a minimum of 1 minute, with a mean of 2.47 minutes. Onset of motor block was comparable in both groups and is found to be statistically insignificant with p value 0.171.

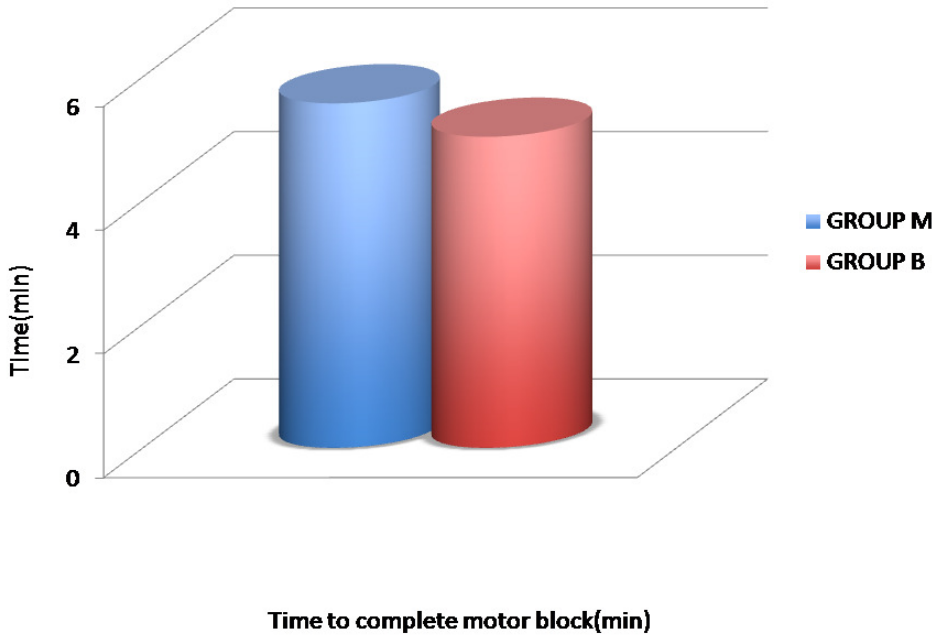


This graph shows the time of onset of motor block between the Group M and Group B

Table 8: Time to complete motor block

	Time to complete motor block (min)	
	Group M	Group B
Mean	5.57	5.03
SD	1.10	0.92
Maximum	8	6
Minimum	4	3
P Value 0.047		

The above table shows the time to achieve complete motor block between the group M and group B and it is found to have an average of 5.57 minutes in group M and 5.03 minutes in group B with SD of 1.10 and 0.92 minutes respectively. Complete motor blockade was achieved earlier in Group B (5.03±0.92 min) than in Group M (5.57±1.10 min) (P=0.047). It is found to be statistically significant.

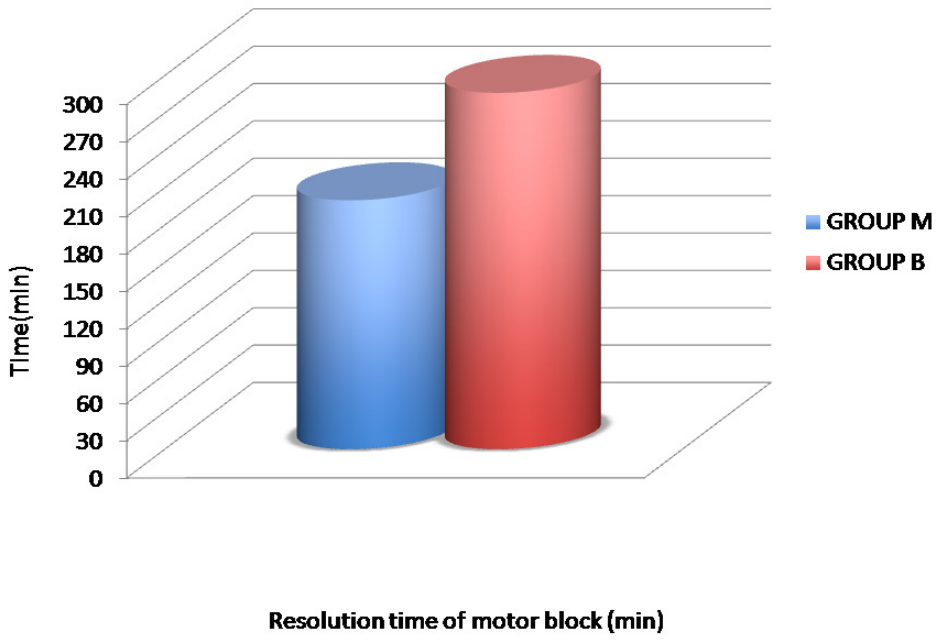


This graph shows the time to complete motor block between the Group M and Group B

Table 9: Resolution time of motor block

	Resolution time of motor block (min)	
	Group M	Group B
Mean	199.77	286.03
SD	38.23	16.90
Maximum	300	322
Minimum	168	260
P Value 0.000		

The above table shows the resolution time of motor block between the group M and group B and it is found to have an average of 199.77 minutes in group M and 286.03 minutes in group B with SD of 38.23 and 16.90minutes respectively.). The resolution time of motor block was significantly prolonged in Group B (286.03±16.90 min) than in Group M (199.77±38.23 min), P=0.000.It is statistically significant.



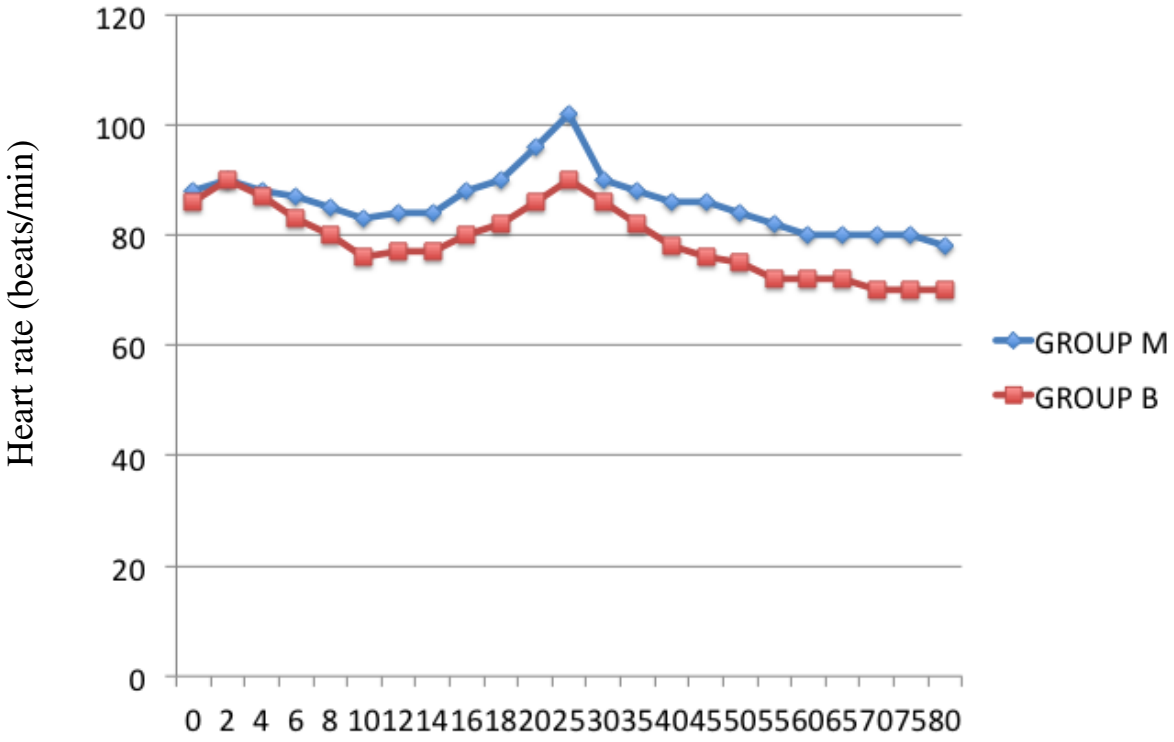
This graph shows the resolution time of motor block between the Group M and Group B

Table 10: Characteristics of sensory and motor block

Variables	Group		P value
	Group M	Group B	
Onset of sensory block (sec)	65.03±10.38	61.93±0.404	0.115
Maximum sensory block height(T) ,median	T4(T3-T5)	T4(T3-T5)	NS
Time to reach maximum cephalad sensory block height (min)	4.57±1.94	3.50±0.97	0.000
Regression time to T10 (min)	162.03±11.62	238.67±27.90	0.000
Total duration of analgesia (min)	322.53±23.24	432.60±64.65	0.000
Onset time of motor block (min)	2.80±1.06	2.47±0.77	0.171
Time to complete motor block (min)	5.57±1.10	5.03±0.92	0.047
Resolution time of motor block (min)	199.77±38.23	286.03±16.90	0.000

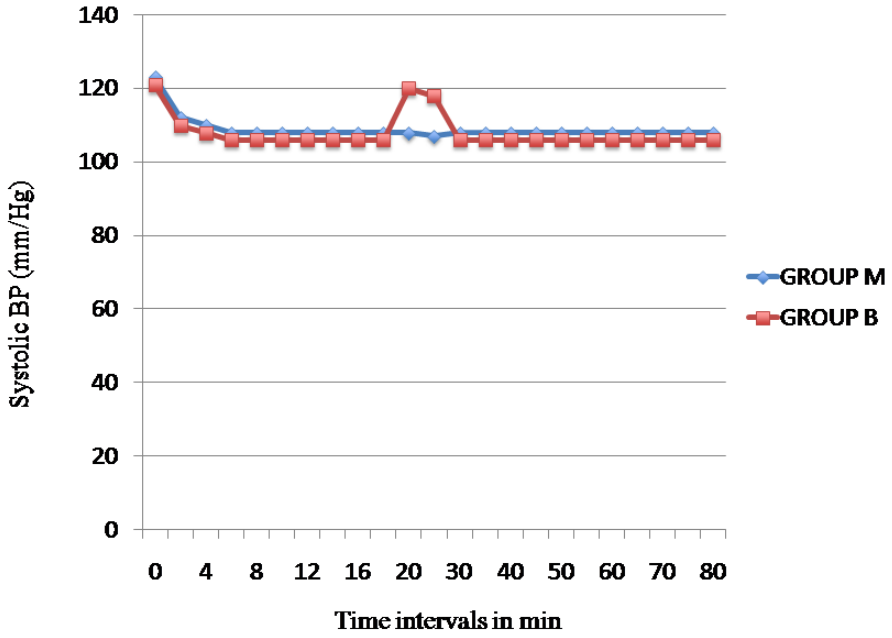
The onset time of sensory and motor block and also the highest level of block achieved (T5) are comparable in both groups [Table 10]. Mean time to reach maximal cephalad-sensory block height was significantly less in Group B (3.50±0.97 min) than in Group M (4.57±1.94 min) with p value of 0.000 and the total duration of analgesia lasted significantly longer in Group B (432.60±64.65 min) as compared to Group M (322.53±23.24 min)(P=0.000). Complete motor blockade was achieved earlier in Group B (5.03±0.92 min) than in GroupM(5.57±1.10 min)(P=0.047).

The resolution time of motor block was significantly prolonged in Group B (286.03±16.90 min) than in Group M (199.77±38.23 min), P=0.000.

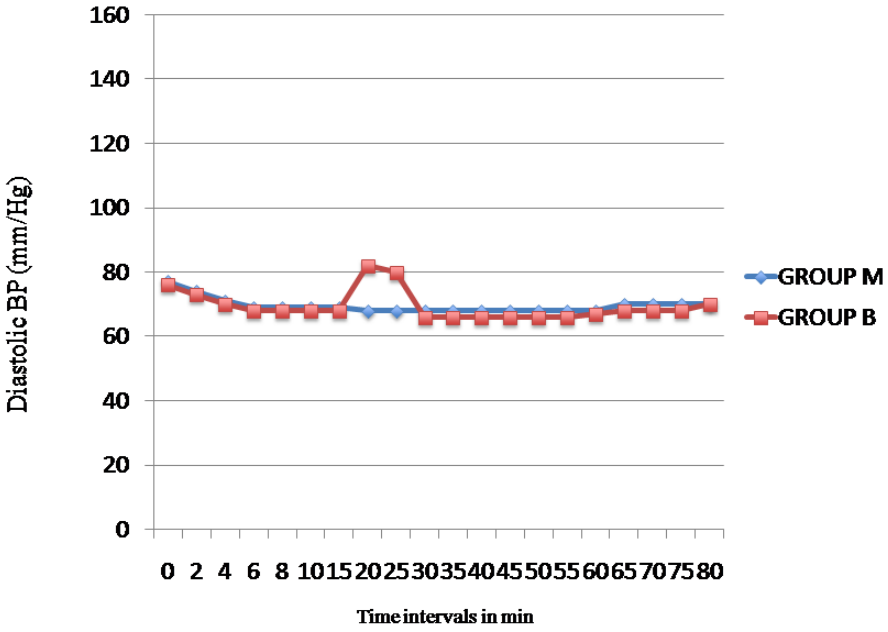


Time intervals in min

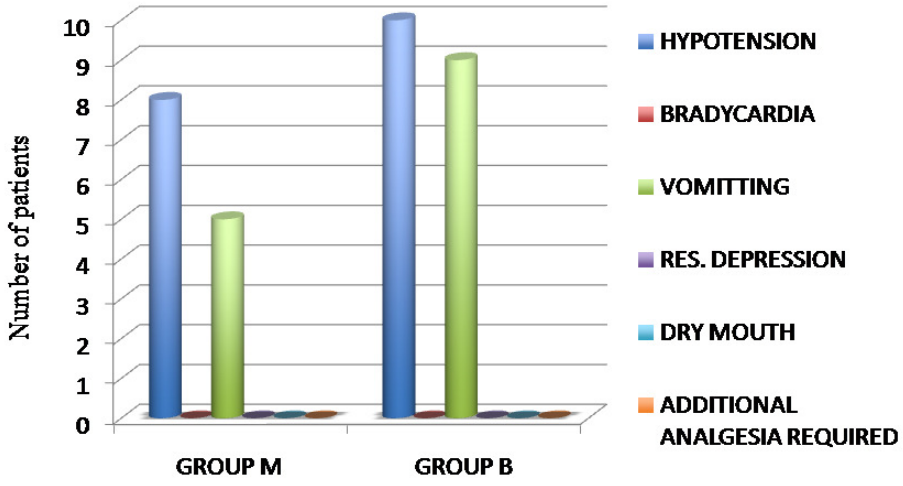
Hemodynamic parameters showed that the lowest values of the HR are after 45 min of the administration of SAB, but none of the patients had bradycardia.



There is a significant fall in SAP at 2 min and 4 min after administration of SAB in both groups.



A significant fall in DAP was seen at 2, 4, 6, and 8 min of administration of SAB. There was an overall trend of fall in SAP and DAP in both groups, except during the time intervals of20 and 25 min (during delivery of baby) where there was rise in both SAP and DAP. The falling trend of arterial blood pressures was more in the Group B than in Group M it is found to be statistically insignificant.



The figure above shows the incidence of complications between the groups M and B and is found to be comparable in both the groups. It is found that hypotension was present in 8(26.7%) and 10(33.3%) of the patients in group M and group B respectively and vasopressor was used in 1 patient among group M and 3 patients in group B. Vomiting was present in 5(16.7%) and 9(30.0%) of the patients respectively.

DISCUSSION

We conducted randomized control study to evaluate the efficacy of premixed versus sequential administration of clonidine as an adjuvant to hyperbaric bupivacaine intrathecally in caesarean section. Background of the study was mixing adjuvants with hyperbaric bupivacaine in a single syringe before injecting the drugs intrathecally is an age old practice. In doing so, the density of the hyperbaric solution and also of the adjuvant drugs may be altered, thus affecting the spread of drugs. Administering local anaesthetic and the adjuvants separately may minimise the effect of the changes in densities

The observation and results obtained in the study are based on the assumption that the original densities of hyperbaric bupivacaine and clonidine are lost when they are premixed in a syringe thus exerting sub optimal actions when compared to sequential manner of administering the drug . Our assumption is supported by the work of **prachee sachan et al** who conducted a randomised contol study in caesarean section by administering intrathecal clonidine with hyperbaric bupivacaine as a mixture and sequential, and **desai et**

al.,[27] Who studied the same effect by adding opioids to local anaesthetic solution intrathecally in caesarean section.

Various authors have used different doses of intrathecal clonidine ranging from 15 mcg to 300 mcg along with local anaesthetics. **kaabachi et al.,**[32] in their study used 2 mcg /kg of intrathecal clonidine and reported extended duration of post operative analgesia, but with moderate side effects. **sethi et al**., [33] used 70 mcg of clonidine and found a significant decrease in mean arterial pressure and heart rate in clonidine group, but no therapeutic intervention was required for either.

A recent study by **ranju singh et al**., [40] on intrthecal clonidine with hyperbaric bupivacaine in caesarean section showed that a dose of 75 mcg clonidine increased the duration of analgesia significantly without increasing maternal side effects.

Similarly **van tuijl et al**., [30] demonstrated that addition of 75 mcg of clonidine to hyperbaric bupivacaine prolongs spinal analgesia and the motor block in caesarean sections without maternal or neonatal side effects. Therefore we used 75 mcg of clonidine and found that it helps achieving a faster block and longer duration of action without worrisome hemodynamic variability or side effects.

The densities of the drugs that we used separately (hyperbaric bupivacaine and clonidine) were 1.0260 and 0.9930, respectively. The density of the mixture of 2 ml (10 mg) of hyperbaric bupivacaine and 0.5 ml (75 mcg) clonidine was also estimated and it was found to be 1.0189.

In our study, we observed that the mean onset time of sensory and motor block was similar in both groups. However, the onset of sensory block does not get any better after a particular dose as supported by a study done by **heo et al.,** [35] who did not report any difference in onset time of sensory or motor block even after using 150 mcg clonidine.

The time to reach maximum sensory block height and a complete motor block was significantly less in Group B (sequential drugs) than in Group M (mixed drugs) in our study. This difference might have existed because of the preferential cephalad spread of clonidine when we administered it through a separate syringe, owing to its hypobaric nature which was lost when the drugs were premixed.

In our study, we found that the mean time taken for sensory block to regress to T10 level was significantly longer in Group B (238.67 ± 27.90 min) than in Group M (162.03 ± 11.62 min) and mean time

taken for motor block regression also significantly longer in Group B (286.03±16.90) than in Group M (199.77±38.23). Similarly, the mean duration of analgesia lasted significantly longer in Group B (432.60 ± 64.65 min) than in Group M (322.53 ± 23.24 min), depicting significant prolongation of analgesic effect in the group receiving drugs in a sequential fashion. This difference might be due to the fact that injecting clonidine and bupivacaine as a mixture dilutes clonidine and receptor occupancy might decrease leading to less pronounced effect. However, if clonidine is administered separately, we expect a greater spread and therefore formation of stronger bonds with the receptor leading to a denser and prolonged block.

According to **desai et al.,** [27] dextrose in a hyperbaric solution slow the movement of morphine molecules in the CSF, reducing the exposure of supraspinal centres to morphine. Clonidine also being hypobaric drug, acting on both spinal and supraspinal receptors, might exhibit similar properties. **Gray et al.,** [36] observed that duration of analgesia is increased when intrathecal morphine is administered with normal saline (hypobaric) than with dextrose saline (hyperbaric).

Activation of post-synaptic alpha-2 receptors in the substantia gelatinosa of the spinal cord is the presumed mechanism by which

clonidine produces analgesia. These receptors are located on primary afferent terminals (both at peripheral and spinal endings), on neurons in the superficial lamina of the spinal cord, and within several brainstem nuclei implicated in analgesia, supporting the possibility of analgesic action at peripheral, spinal, and brainstem sites.

Clonidine decreases heart rate by a presynaptic mediated inhibition of nor epinephrine release and by a direct depression of atrioventricular nodal conduction after systemic absorption. The maximum fall in the heart rate when compared to the baseline was 19% in Group B, whereas it was only 12% in Group M which was statistically significant ($P < 0.001$). This fall in heart rate was more pronounced after about 40-60 min of administration of subarachnoid block and toward end of the surgery. However, in our study none of the patients had bradycardia.

A significant fall in arterial blood pressure after subarachnoid block was observed in our study. The fall from baseline SAP and DAP in Group M was 10% and 14% and in Group B was 8% and 13%, respectively. Haemodynamic effects of clonidine after neuraxial or systemic administration begin within 30 min, reach maximum within 1-2 h, and last approximately 6-8 h after a single injection. We

observed hypotension in 26.7% of patients in group M and 33.3% of patient in group B. Hypotension was managed by i.v fluids and vasopressors were needed for only 1% and 3% parturients in Groups M and B, respectively which was comparable in both groups, suggesting that the clonidine groups did not have a higher predisposition for the development of significant hypotension if administered sequentially than mixed groups. In our study, the level of sedation provided by intrathecal clonidine (RSS 2 and 3) was not only acceptable, but also beneficial owing to its anxiolytic role.

None of the patients needed any additional analgesics during the intra-operative period. In line with our observations, **Benhamou et al**. [22] found that when intrathecal clonidine was administered with hyperbaric bupivacaine, none of patients required additional analgesics to obtain an adequate sensory block. None of the patients complained of dry mouth.

There was no incidence of hypotension, bradycardia and nausea/vomiting, neurological deficit, prolonged sedation in the post-operative period.

The APGAR scores in our study were statistically comparable in both groups. **Benhamou et al.** [22] and **Neves et al**. [39] also concluded that addition of intrathecal clonidine did not adversely affect the neonatal outcome in terms of APGAR scores.

In our study we, measured the densities of solutions in vitro but, we could not measure the densities when injected into the CSF. Hence, we could not assess what actually happens to the drug densities intrathecally. Similarly, effects of temperature of drugs when injected were not considered.

SUMMARY

Sixty parturients of ASA 1&2 undergoing elective caesarean section under spinal anaesthesia were enrolled in this randomised controlled study. They were equally and randomly allocated into two groups of 30 each namely Group M and Group B.

Patients in Group M received 10mg of 0.5%hyperbaric bupivacaine with clonidine 75 microgram as a mixture in single syringe. Patients in Group B received clonidine 75 microgram followed by hyperbaric bupivacaine 10mg in different syringes.

They were observed for onset and duration of sensory and motor block, total duration of analgesia ,hemodynamic changes, neonatal outcome, sedation and adverse effects. The collected data was analysed using independent t test and a p value <o.o5 was significant.

Sequential administration of clonidine reduces the time to achieve complete motor and maximum sensory block and significantly prolongs total duration of analgesia without any significant adverse effect like sedation, hypotension or bradycardia or dryness as compared to the administration as a mixture of bupivacaine and clonidine.

CONCLUSION

Sequential administration of clonidine reduces the time to achieve complete motor and maximum sensory block and significantly prolongs total duration of analgesia when compared to mixture of hyperbaric bupivacaine and clonidine. Addition of clonidine to hyperbaric bupivacaine provide dense surgical anaesthesia without any significant maternal and neonatal adverse outcomes, and without any significant unwanted side effects.

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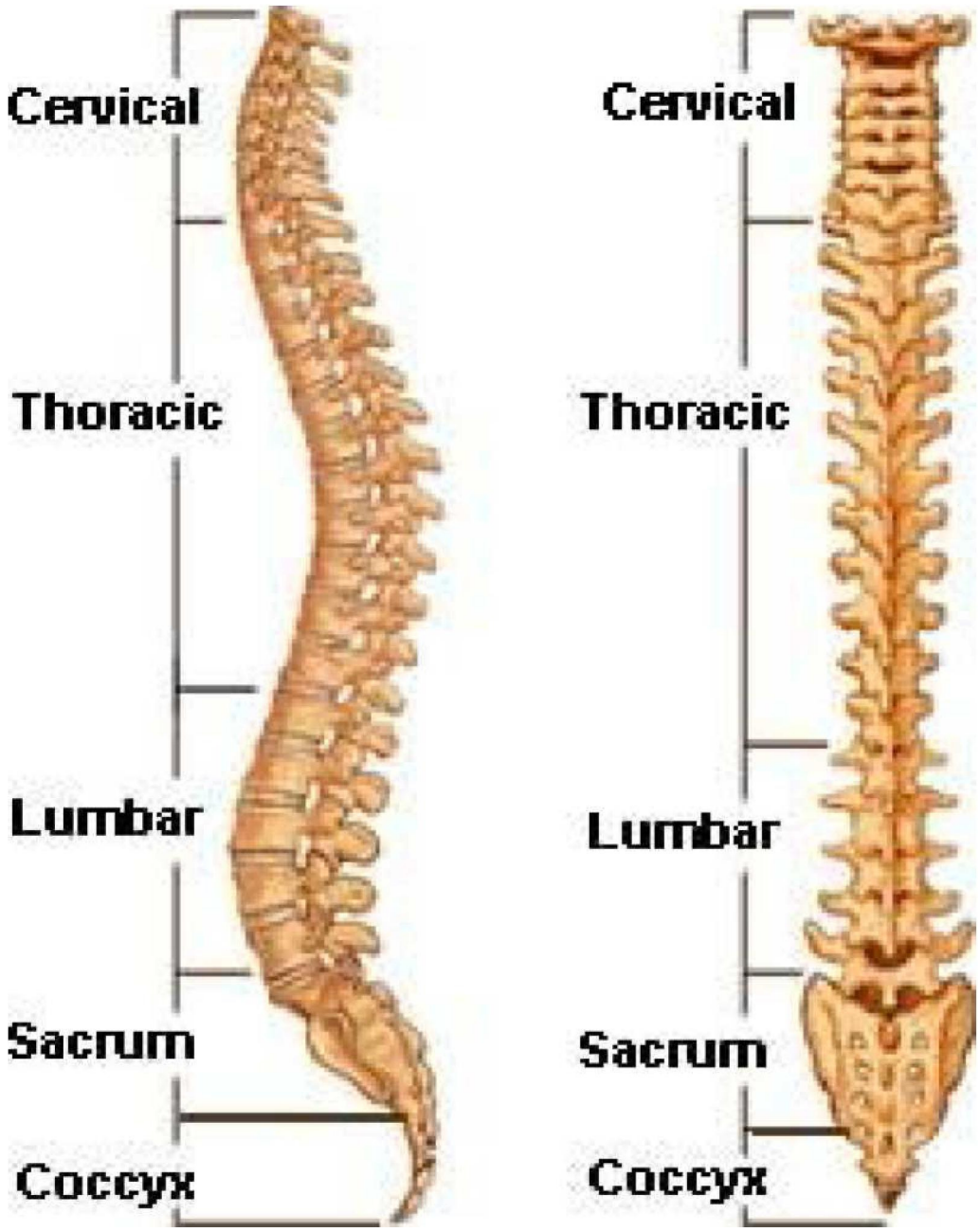


Fig.1 : VERTEBRAL COLUMN

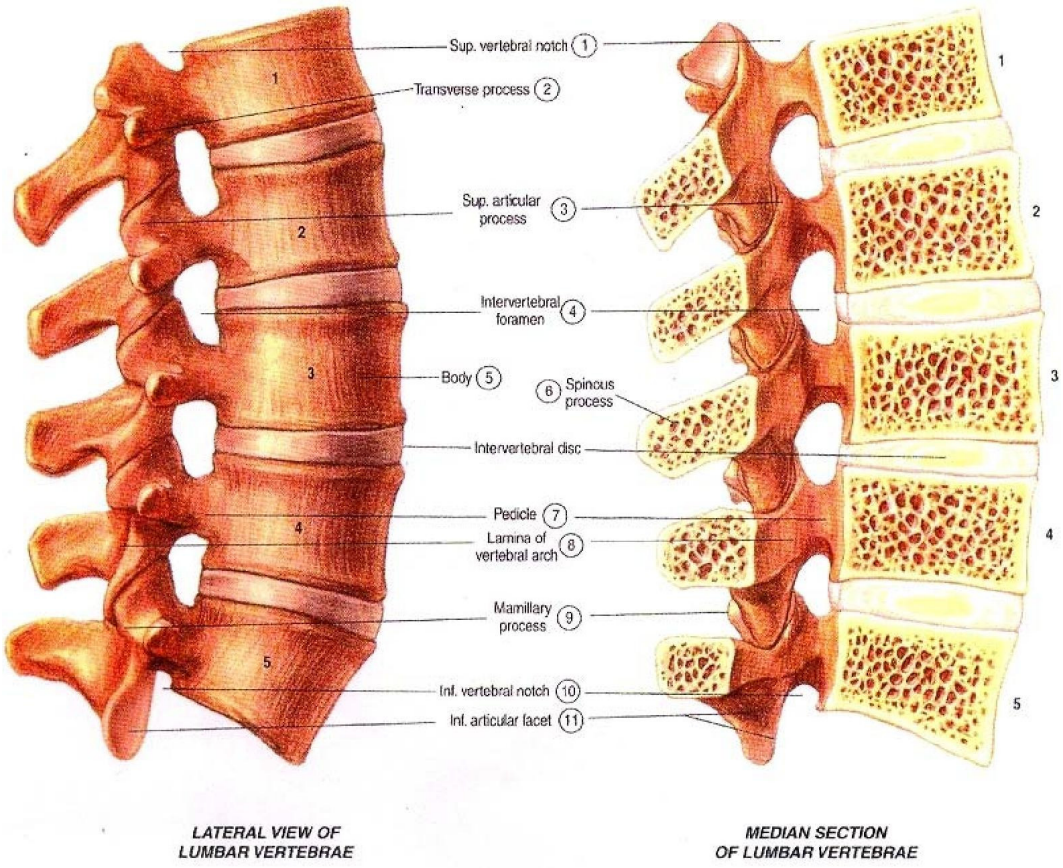


FIG2 LATERAL VIEW OF LUMBAR VERTEBRAL COLUMN

Cross and longitudinal section

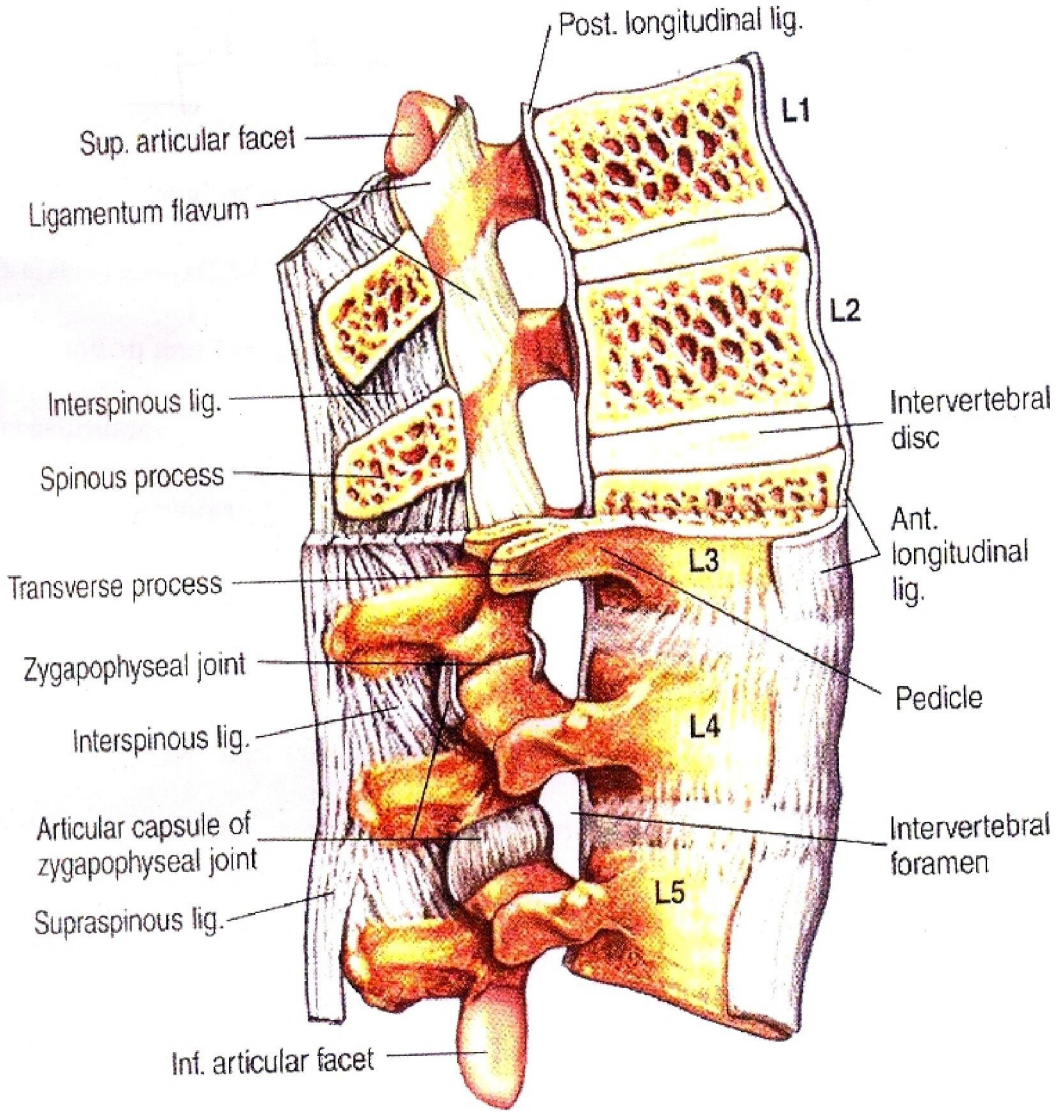


FIG 6.: VERTEBRAL LIGAMENTS

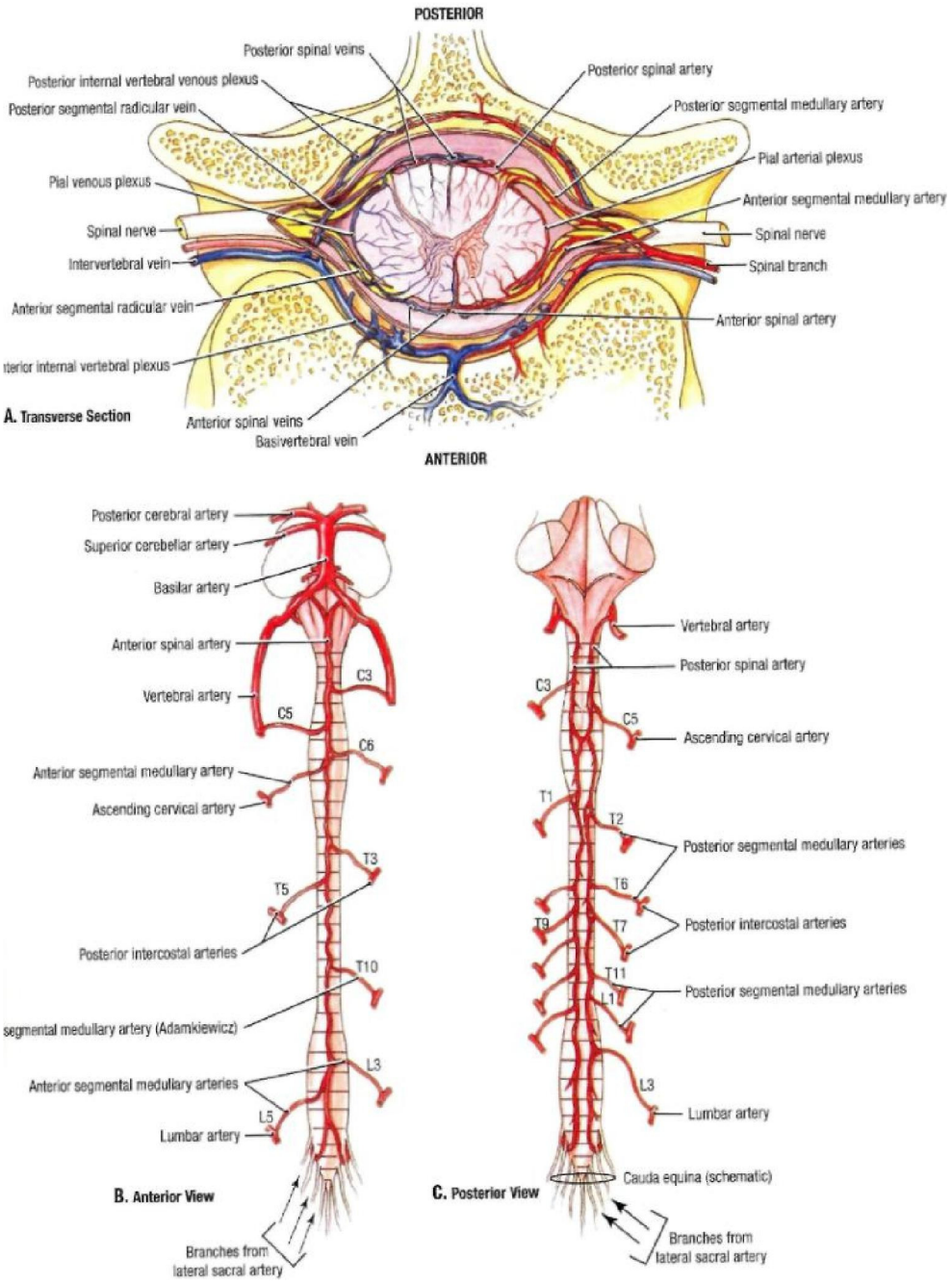


FIG –7: BLOOD SUPPLY OF THE SPINAL CORD

PROFORMA

Name: Age/Sex: IP No:

ASA Physical status: Date:

Pre Operative:

General examinations:

PR : CVS :

BP : RS :

RR : SPO_2 :

Diagnosis :

Proposed surgery :

Premedication : Tab. Ranitidine 150mg Night & Morning prior to surgery

Group B/Group M

Time of subarachnoid injection :

Onset time of sensory block(secs) :

Height of maximum sensory block :

Time to reach maximum sensory block(mts) :

Regression time to T_{10}(mts) :

Total duration of analgesia (mts) :

Onset Time of motor block (mts) :

Time to complete motor block (mts) :

Resolution time of motor block(mts) :

Intra operative hemodynamics

Mts	0	2	4	6	8	10	12	14	16	18	20	25	30	35	40	45	50	55	60	65	70	75
HR																						
SBP																						
DBP																						

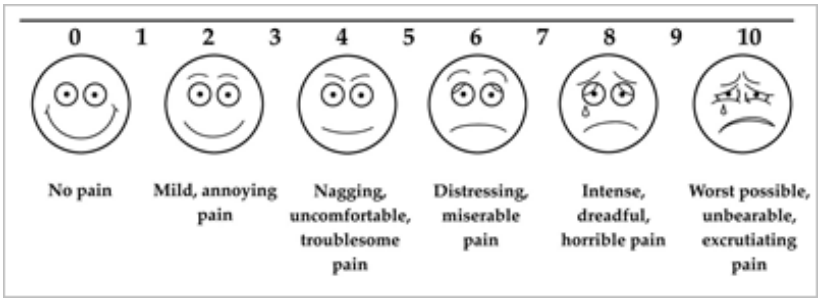
Sedation score(until 2hr Post operatively)

Level 1 : Awake, anxious Level 4 : Brisk response to stimuli

Level 2 : Awake, tranquil Level 5 : Suggish response to stimuli

Level 3 Responds to commands Level 6 : No response

Post operative VAS score:



Side effects

Badycardia Hypotension

Nausea & Vomiting Sedation

S.NO	1	2	3	4	5	6	7	8	9	10	11
TYPE OF INTERVENTION	M	B	M	B	B	M	M	B	M	M	B
AGE (YEARS)	25	28	23	29	24	24	21	21	31	25	26
WEIGHT (KGS)	60	65	58	64	56	57	56	57	62	65	61
HEIGHT (CMS)	156	160	155	156	160	148	150	152	156	165	154
DURATION OF SURGERY (SEC)	55	78	78	82	80	78	84	80	79	84	80
ONSET OF SENSORY BLOCK (SEC)	90	60	40	65	60	70	60	60	60	64	65
MAXIMUM HEIGHT OF SENSORY BLOCK	T6	T4	T6	T4	T6	T6	T5	T4	T5	T6	T4
TIME TO REACH MAXIMUM BLOCK (MIN)	7	2	4	3	5	5	5	2	4	4	3
REGRESSION TIME (MIN)	150	258	153	222	250	150	150	244	155	170	262
TOTAL DURATION OF ANALGESIA (MIN)	310	337	300	450	466	360	310	355	350	360	322
ONSET OF MOTOR BLOCK (MIN)	2	3	1	2	4	3	2	2	3	2	3
TIME TO COMPLETE MOTOR BLOCK (MIN)	8	6	4	5	6	7	5	3	5	4	5
RESOLUTION TIME (MIN)	180	267	200	278	260	300	200	322	272	280	298
SYSTOLIC BP (mm Hg)	125	118	126	125	110	129	116	110	125	120	120
DIASTOLIC BP (mm Hg)	67	68	80	81	70	81	70	80	81	78	70
PULSE RATE	70	91	106	90	94	116	97	88	107	91	82
SpO_2(%)	98	98	99	99	98	99	98	99	98	97	99
HYPOTENSION	yes	yes	no	no	yes	no	no	yes	no	no	yes
VASOPRESSOR USE	no	no	no	no	yes	no	no	yes	no	no	yes
BRADYCARDIA	no	no	no	no	no	no	no	no	no	no	no
VOMITING	yes	no	no	no	yes	no	no	no	no	no	no
RESPIRATORY DEPRESSION	no	no	no	no	no	no	no	no	no	no	no
DRY MOUTH	no	no	no	no	no	no	no	no	no	no	no
ADDITIONAL ANALGESIA USED	no	no	no	no	no	no	no	no	no	no	no

12	M	30	62	155	80	62	T4	4	153	337	2	6	190	110	70	78	99	yes	no	no	no	no	no	no
13	B	25	60	157	81	60	T4	3	240	470	2	4	290	126	78	86	98	no	no	no	no	no	no	no
14	B	27	58	159	78	65	T6	4	256	450	2	4	300	130	78	89	99	no	no	no	no	no	no	no
15	M	25	61	155	82	70	T6	3	170	350	2	4	190	126	72	98	99	no	no	no	no	no	no	no
16	M	30	62	162	82	72	T4	3	180	322	3	6	178	124	76	99	99	yes	no	no	no	no	no	no
17	B	27	58	156	80	62	T4	3	250	480	2	6	300	120	80	76	98	yes	no	no	no	no	no	no
18	M	24	56	156	80	68	T5	5	166	300	4	6	176	132	86	78	99	no	no	no	no	no	no	no
19	B	29	61	165	79	60	T6	4	250	500	3	5	287	128	82	86	99	no	no	no	no	no	no	no
20	M	24	56	156	80	68	T5	6	178	300	4	6	176	132	86	78	99	yes	yes	no	yes	no	no	no
21	B	22	58	152	79	60	T4	3	163	315	2	4	312	118	74	84	99	no	no	no	yes	no	no	no
22	B	27	64	166	81	62	T6	2	164	317	2	3	266	128	68	92	98	no	no	no	no	no	no	no
23	M	26	62	156	80	74	T4	4	176	290	4	5	168	128	72	78	99	no	no	no	no	no	no	no
24	B	28	60	157	81	65	T4	3	233	470	2	4	290	126	78	84	98	no	no	no	no	no	no	no
25	B	24	56	160	80	60	T6	5	250	466	4	5	260	120	70	94	98	yes	yes	no	yes	no	no	no
26	B	22	57	258	85	60	T4	3	240	490	1	4	278	124	76	78	99	yes	yes	no	no	no	no	no
27	M	26	58	160	82	68	T5	6	166	300	3	5	170	122	76	82	99	no	no	no	yes	no	no	no
28	B	23	59	157	86	60	T4	3	255	444	2	5	300	126	88	86	98	yes	yes	no	yes	no	no	no
29	B	25	60	157	81	60	T4	3	240	470	2	5	290	126	78	86	98	no	no	no	no	no	no	no
30	B	25	60	157	81	60	T4	3	240	470	2	5	290	126	78	86	98	no	no	no	no	no	no	no
31	M	31	56	156	80	68	T5	5	166	300	4	6	176	132	86	78	99	no	no	no	no	no	no	no
32	M	32	62	167	84	72	T4	5	188	342	3	6	180	128	80	86	99	no	no	no	no	no	no	no
33	M	24	56	156	80	68	T6	5	160	312	4	6	190	110	78	78	99	yes	no	no	no	no	no	no
34	B	29	58	156	80	62	T6	5	240	480	2	6	300	120	80	76	98	yes	no	no	no	no	no	no
35	B	26	61	154	80	65	T4	4	262	322	3	5	298	120	70	82	99	yes	yes	no	yes	no	no	no
36	B	24	56	160	80	60	T6	3	250	466	4	6	260	110	76	94	98	yes	yes	no	yes	no	no	no
37	M	32	62	167	84	72	T4	5	188	342	3	6	180	128	80	86	99	no	no	no	no	no	no	no
38	B	28	65	160	78	60	T4	5	258	337	3	6	267	118	68	91	98	yes	no	no	no	no	no	no
39	B	27	58	156	80	62	T4	2	250	480	2	6	300	120	80	76	98	yes	no	no	no	no	no	no

40	M	24	58	155	78	40	T6	3	153	345	1	4	200	126	80	106	99	no	no	no	no	no	no	no
41	M	31	64	160	86	65	T4	5	166	345	3	6	176	120	80	78	99	no	no	no	no	no	no	no
42	M	25	58	162	80	68	T5	6	154	300	4	7	189	124	76	88	99	no	no	no	no	no	no	no
43	B	29	64	156	82	65	T4	4	222	450	2	5	278	125	81	90	99	no	no	no	no	no	no	no
44	B	30	61	154	80	65	T4	5	262	500	3	6	298	120	70	82	99	yes	yes	no	yes	no	no	no
45	M	21	56	150	84	60	T5	5	150	310	2	5	200	116	70	97	98	no	no	no	no	no	no	no
46	M	27	65	156	84	60	T4	3	158	337	1	5	186	136	80	88	99	yes	no	no	no	no	no	no
47	M	25	58	148	84	64	T6	2	170	360	2	4	280	120	78	91	97	no	no	no	no	no	no	no
48	M	24	56	156	80	68	T5	5	166	300	4	6	176	122	70	78	99	no	no	no	no	no	no	no
49	B	21	58	159	78	65	T6	4	256	450	2	5	300	130	78	89	99	no	no	no	no	no	no	no
50	B	27	58	156	80	62	T4	3	250	480	2	6	300	120	80	76	98	yes	no	no	no	no	no	no
51	M	31	62	156	79	60	T5	2	155	350	3	5	272	125	81	107	98	no	no	no	no	no	no	no
52	M	29	60	152	80	68	T6	5	153	300	4	6	176	120	72	78	99	yes	no	no	yes	no	no	no
53	B	20	64	156	82	65	T4	4	222	450	2	5	278	125	81	90	99	no	no	no	no	no	no	no
54	M	23	58	155	78	40	T6	6	153	300	1	4	200	126	80	106	99	no	no	no	no	no	no	no
55	M	24	56	156	80	68	T5	5	166	300	4	6	176	132	86	78	99	no	no	no	no	no	no	no
56	M	25	60	156	55	76	T6	5	150	310	2	8	180	125	67	70	98	yes	no	no	yes	no	no	no
57	B	33	58	152	79	63	T6	3	163	488	2	4	287	118	74	84	99	no	no	no	yes	no	no	no
58	B	28	65	160	78	60	T4	4	258	337	3	6	267	118	68	91	98	yes	no	no	no	no	no	no
59	B	24	56	160	80	60	T6	5	250	466	4	6	260	110	70	94	98	yes	yes	no	yes	no	no	no
60	M	24	56	156	80	68	T4	5	148	334	4	6	176	110	70	78	99	no	no	no	no	no	no	no